A STUDY ON EPIDEMIOLOGY, ANTIBIOTIC SUSCEPTIBILITY AND THE IMPACT OF APPROPRIATE INITIAL ANTIBIOTIC THERAPY ON THE CLINICAL OUTCOME OF GRAM NEGATIVE BACTERAEMIA IN A TERTIARY CARE HOSPITAL

Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical University, Chennai

In fulfillment of the requirements for the award of the degree of

Doctor of Medicine in General Medicine

Under the guidance of

Dr. TOLSTOY .R, M.D.,

DEPARTMENT OF GENERAL MEDICINE

P.S.G INSTITUTE OF MEDICAL SCIENCES & RESEARCH, COIMBATORE

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY,

CHENNAI, TAMIL NADU

APRIL 2017

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled, **"A STUDY ON EPIDEMIOLOGY, ANTIBIOTIC SUSCEPTIBILITY AND THE IMPACT OF APPROPRIATE INITIAL ANTIBIOTIC THERAPY ON THE CLINICAL OUTCOME OF GRAM NEGATIVE BACTERAEMIA IN A TERTIARY CARE HOSPITAL"** is the bonafide original work of **Dr. VINU B,** done under my direct guidance and supervision in the Department of General Medicine, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations by The Tamilnadu Dr. MGR Medical University, Chennai for the degree of Doctor of Medicine in General Medicine.

Signature of the guide

Dr. TOLSTOY .R, M.D.,
Professor of Medicine,
Department of General Medicine,
PSG IMS&R, Coimbatore.

CERTIFICATE BY THE HOD, DEAN OF THE INSTITUTION

This is to certify that the dissertation entitled, "**A STUDY ON EPIDEMIOLOGY, ANTIBIOTIC SUSCEPTIBILITY AND THE IMPACT OF APPROPRIATE INITIAL ANTIBIOTIC THERAPY ON THE CLINICAL OUTCOME OF GRAM NEGATIVE BACTERAEMIA IN A TERTIARY CARE HOSPITAL"** is the bonafide original research work of **Dr. VINU B** under the guidance of **Dr. TOLSTOY. R, M.D.**, Professor of Medicine, PSG IMS&R, Coimbatore in partial fulfillment of the requirements for the degree of Doctor of Medicine in General Medicine.

Seal and Signature of the HOD
Dr. K. JAYACHANDRAN,M.D.,
Professor and HOD,
Department of Medicine
PSG IMS & R, Coimbatore

Seal and Signature of the Dean
Dr. RAMALINGAM .S, M.D.,
Dean
PSG IMS & R, Coimbatore

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled "**A STUDY ON EPIDEMIOLOGY, ANTIBIOTIC SUSCEPTIBILITY AND THE IMPACT OF APPROPRIATE INITIAL ANTIBIOTIC THERAPY ON THE CLINICAL OUTCOME OF GRAM NEGATIVE BACTERAEMIA IN A TERTIARY CARE HOSPITAL"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. TOLSTOY .R, M.D.,** Professor of Medicine, PSG IMS&R, Coimbatore.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University in fulfillment of the University regulations for the award of Doctor of Medicine degree in General Medicine. This dissertation has not been submitted for award of any other degree or diploma.

Signature of the Candidate

Dr . VINU B

ACKNOWLEDGEMENT

I am much obliged to my research guide Professor Dr. Tolstoy. R, MD., Professor, Department of General Medicine, for giving me confidence and motivation throughout the study.

I feel grateful and thankful to Professor Dr. Murali. A,MD., for being a great inspiration which motivated me to go an extra mile . I am very much thankful for his constant inspiration and timely suggestions without which this study would have not been completed.

I would also extend my gratitude to Professor Dr.Jayalakshmi.J, Department of Microbiology, for her constant encouragement and structural support in carrying out this study.

I am forever thankful to Professor. Dr.Jayachandran K, Professor and HOD, Department of General Medicine, for his concern and constant supervision during the study tenure.

I also thank Professor Dr.Sujaya Menon, M.D, MRCP, Professor Dr.Saravanan, M.D, Professor Dr.L.S.Somasundaram M.D, Professor Dr.S.Sujith Kumar, Department of General Medicine for their support and encouragement.

My heartful thanks to Dr.Anith Kumar M.D, MRCP, Dr.Denesh Narasimham M.D, Associate Professor, Department of General Medicine for their support and guidance.

I also thank Dr. Yoganathan M.D,, Dr. Srinivasan M.D,, Dr. Zeya Ansari M.D,, Dr.Santni M.D, Dr.Vellammal M.D, Dr.Sathish M.D, Assistant professors, Department of General medicine for their support.

I also extend my thanks to all my colleague post graduates and my friends for their help and cooperation during the study.

I also thank all the staff of Department of General Medicine, Department of Microbiology for their help in carrying out the study.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee
Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

To
Dr B Vinu
Postgraduate
Department of General Medicine
PSG IMS & R
Coimbatore

Ref: Project No. 14/437

Date: March 30, 2015

Dear Dr Vinu,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 12.12.2014 to conduct the research study entitled "*Study on epidemiology, antibiotic susceptibility and the impact of appropriate initial antibiotic therapy on the clinical outcome of gram negative bacteraemia in a tertiary care hospital*" during the IHEC meeting held on 22.12.2014.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol
3. Informed consent form
4. Data collection tool
5. Permission letter from concerned Head of the Department
6. Current CVs of Principal investigator, Co-investigator
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 22.12.2014 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. P. Sathyan (Chairperson, IHEC)	DO, DNB	Clinician (Ophthalmology)	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr. S.Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Mrs P Rama	M Pharm	Non-medical (Pharmacy)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP /ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee
Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
    a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
    b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
    c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
    d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
    e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
    f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

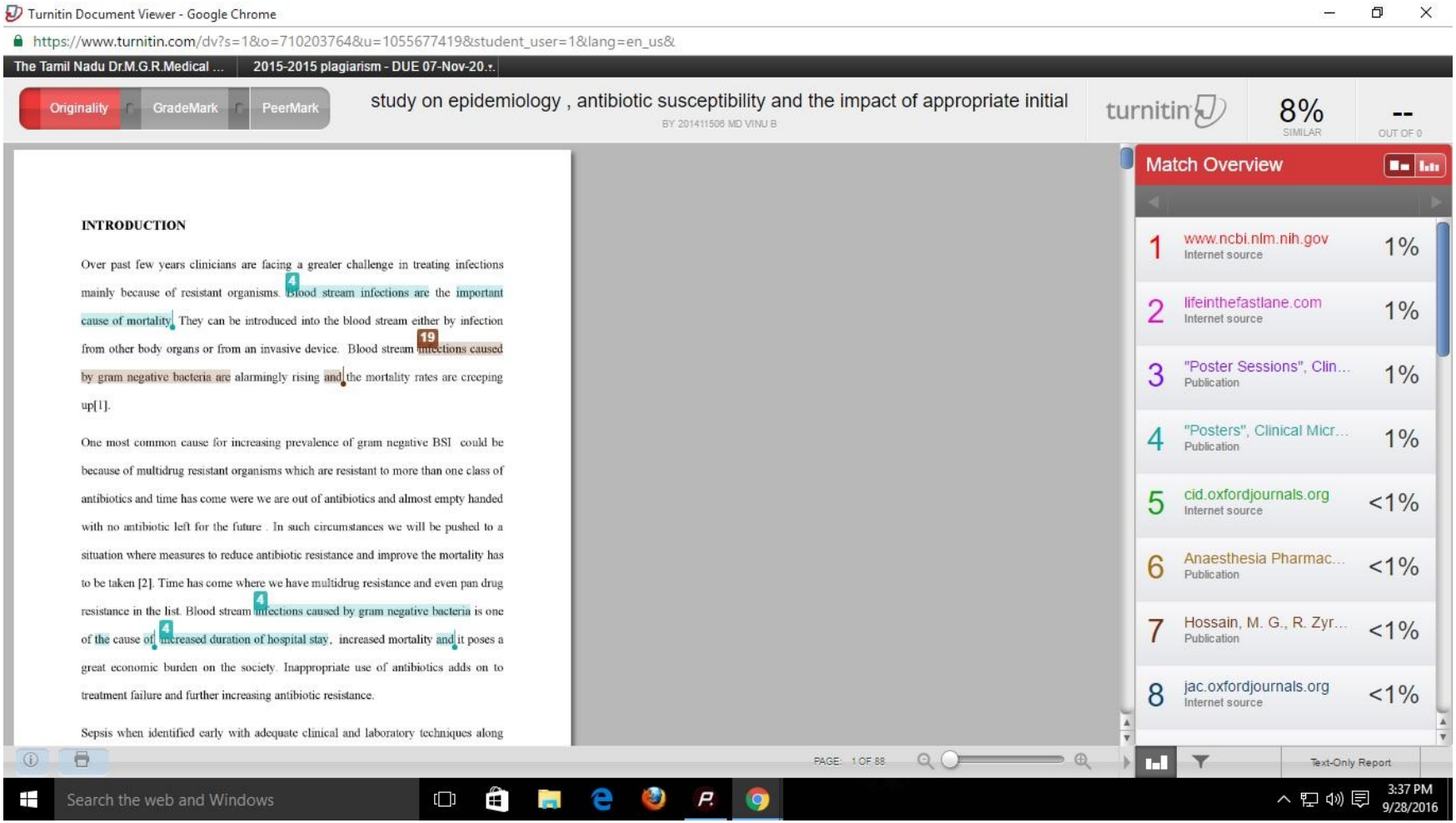
Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

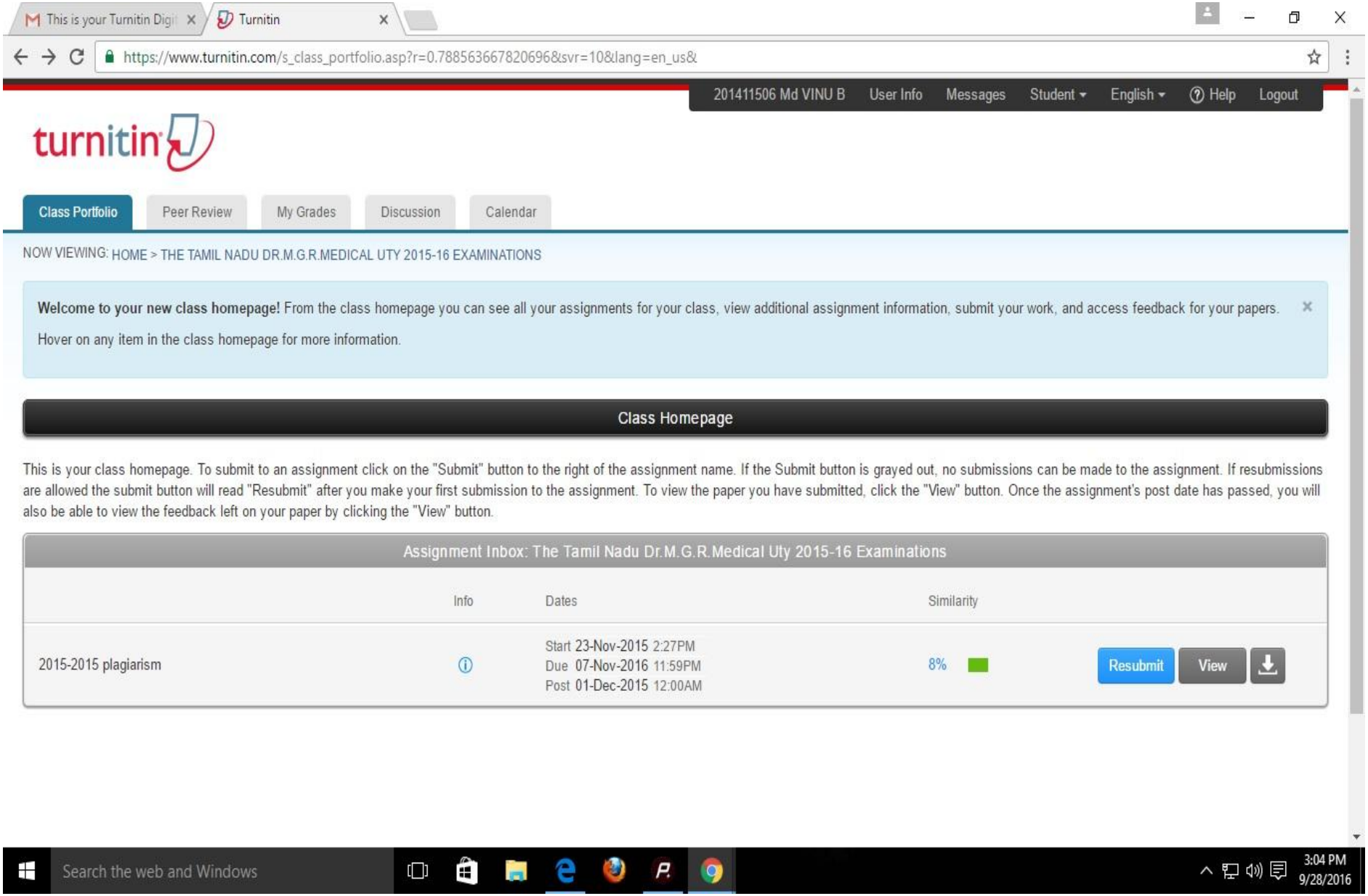
Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member-Secretary
Institutional Human Ethics Committee


Turnitin Document Viewer - Google Chrome
https://www.turnitin.com/dv?s=1&o=710203764&u=1055677419&student_user=1&lang=en_us&
The Tamil Nadu Dr.M.G.R.Medical ...
2015-2015 plagiarism - DUE 07-Nov-20...
Originality
GradeMark
PeerMark
study on epidemiology , antibiotic susceptibility and the impact of appropriate initial
BY 201411506 MD VINU B
turnitin
8%
SIMILAR
--
OUT OF 0
INTRODUCTION
Over past few years clinicians are facing a greater challenge in treating infections mainly because of resistant organisms. Blood stream infections are the important cause of mortality. They can be introduced into the blood stream either by infection from other body organs or from an invasive device. Blood stream infections caused by gram negative bacteria are alarmingly rising and the mortality rates are creeping up[1].
One most common cause for increasing prevalence of gram negative BSI could be because of multidrug resistant organisms which are resistant to more than one class of antibiotics and time has come were we are out of antibiotics and almost empty handed with no antibiotic left for the future . In such circumstances we will be pushed to a situation where measures to reduce antibiotic resistance and improve the mortality has to be taken [2]. Time has come where we have multidrug resistance and even pan drug resistance in the list. Blood stream infections caused by gram negative bacteria is one of the cause of increased duration of hospital stay, increased mortality and it poses a great economic burden on the society. Inappropriate use of antibiotics adds on to treatment failure and further increasing antibiotic resistance.
Sepsis when identified early with adequate clinical and laboratory techniques along
Match Overview
1 www.ncbi.nlm.nih.gov Internet source 1%
2 lifeinthefastlane.com Internet source 1%
3 "Poster Sessions", Clin... Publication 1%
4 "Posters", Clinical Micr... Publication 1%
5 cid.oxfordjournals.org Internet source <1%
6 Anaesthesia Pharmac... Publication <1%
7 Hossain, M. G., R. Zyr... Publication <1%
8 jac.oxfordjournals.org Internet source <1%
PAGE: 1 OF 88
Text-Only Report
Search the web and Windows
3:37 PM
9/28/2016


This is your Turnitin Digi
Turnitin
https://www.turnitin.com/s_class_portfolio.asp?r=0.788563667820696&svr=10&lang=en_us&
201411506 Md VINU B
User Info
Messages
Student
English
Help
Logout
turnitin
Class Portfolio
Peer Review
My Grades
Discussion
Calendar
NOW VIEWING: HOME > THE TAMIL NADU DR.M.G.R.MEDICAL UTY 2015-16 EXAMINATIONS
Welcome to your new class homepage! From the class homepage you can see all your assignments for your class, view additional assignment information, submit your work, and access feedback for your papers.
Hover on any item in the class homepage for more information.
Class Homepage
This is your class homepage. To submit to an assignment click on the "Submit" button to the right of the assignment name. If the Submit button is grayed out, no submissions can be made to the assignment. If resubmissions are allowed the submit button will read "Resubmit" after you make your first submission to the assignment. To view the paper you have submitted, click the "View" button. Once the assignment's post date has passed, you will also be able to view the feedback left on your paper by clicking the "View" button.
Assignment Inbox: The Tamil Nadu Dr.M.G.R.Medical Uty 2015-16 Examinations
Info
Dates
Similarity
2015-2015 plagiarism
Start 23-Nov-2015 2:27PM
Due 07-Nov-2016 11:59PM
Post 01-Dec-2015 12:00AM
8%
Resubmit
View
Search the web and Windows
3:04 PM
9/28/2016

CONTENTS

INTRODUCTION

Over past few years clinicians are facing a greater challenge in treating infections mainly because of resistant organisms. Blood stream infections are the important cause of mortality. They can be introduced into the blood stream either by infection from other body organs or from an invasive device. Blood stream infections caused by gram negative bacteria are alarmingly rising and the mortality rates are creeping up[1].

One most common cause for increasing prevalence of gram negative BSI could be because of multidrug resistant organisms which are resistant to more than one class of antibiotics and time has come were we are out of antibiotics and almost empty handed with no antibiotic left for the future . In such circumstances we will be pushed to a situation where measures to reduce antibiotic resistance and improve the mortality has to be taken [2]. Time has come where we have multidrug resistance and even pan drug resistance in the list. Blood stream infections caused by gram negative bacteria is one of the cause of increased duration of hospital stay, increased mortality and it poses a great economic burden on the society. Inappropriate use of antibiotics adds on to treatment failure and further increasing antibiotic resistance.

Sepsis when identified early with adequate clinical and laboratory techniques along with appropriate antibiotic may reduce treatment failure to manifold [3]. All these calls into action for an antibiotic policy and antibiotic stewardship which helps us to overcome the hindrances faced during treatment

and treatment outcome in terms of mortality. When such policies are adapted many aspects attributing to treatment failure like misuse of antibiotics in the form of inappropriate selection, inappropriate dose and inappropriate duration can be prevented.

In the past few years the discovery of new antibiotics slowed down which could be attributed to one of the following reasons. First is the technical challenge in discovering newer antibiotic because of the acquired resistance in GNB. Second could be the regulatory policies on new antibiotics which have become more complex and third is the fact that antibiotics are prescribed only for a short course unlike for other chronic ailments hence they are less lucrative [3].

Several advances have been made so far in diagnosing bacterial pathogens but this has become less feasible in many of the countries, leading to delay in diagnosis [4]. We still lack evidence on the effect of antibiotic resistance on outcome of infection. Greatest challenge is that patients infected by these resistant pathogens would have already been exposed to multiple antibiotics, suffer from chronic ailments, old age or immuno compromised hence all these factors confound in determining the clinical outcome.

One of the important factors for development of antibiotic resistance is the use of broad spectrum antibiotics for severe infections especially in ICU settings. This is one of the daily challenges because development of newer and newer antibiotics could not keep up with emerging antibiotic resistance [5].

Among the gram negative organisms, blood stream infections caused by gram negative organisms like E. coli and K. pneumoniae are most commonly reported [6].

Earlier it has been reported that E.coli was a community acquired pathogen causing blood stream infections which was sensitive to third generation cephalosporin. These pathogens have now acquired many resistant strains like ESBL, AmpC and many more in the list. Nowadays these resistant organisms are reported as community acquired as well. Hence opting for a suitable antibacterial agent is of prime importance in such serious infections [7].

In this study we have evaluated the clinical outcome of gram negative bacteremia and the effect of appropriateness of empirical antibiotic started on clinical outcome and also we have analyzed the microbiological profile of gram negative bacteria in our hospital so that it would help us in understanding the epidemiology and the antibiogram of gram negative bacteria in our hospital which will enable us to update the existing hospital policy which will have a significant impact on both morbidity and mortality.

AIMS AND OBJECTIVES

PRIMARY OUTCOME

- To assess the clinical outcome of gram negative bacteraemia.
- To assess the microbiological profile and susceptibility pattern of gram negative bacteria**.**

SECONDARY OUTCOME

- To evaluate the impact of appropriateness of empirical antibiotic of choice and its impact on treatment outcome.
- To determine the time taken to institute first dose of antibiotic after clinical suspicion of sepsis and its relation to clinical outcome.
- Duration of antibiotic and its impact on clinical outcome.
- Clinical outcome of various gram negative bacteria.

STUDY DESIGN

A prospective observational study on patients with Gram-negative bacteraemia during a 12 month period from June 2015 to June 2016 in patients admitted to medical wards and medical ICU .

SAMPLE SIZE - 60

INCLUSION CRITERIA

- Age > 18 years.
- All Patients admitted in general medical ward/ medical ICU with sepsis due to Gram-negative bacteraemia (1or more positive blood cultures).
- Polymicrobial infections would also be included if at least one Gram-negative organism was present.

. EXCLUSION CRITERIA

- Age less than 18years.
- Blood culture positive Salmonella typhi and paratyphi A &B.
- Subsequent episodes of bacteraemia in study patients.
- Patients with Chronic kidney disease, Chronic liver disease, patients on corticosteroids, Malignancy, Severe neurological disease, HIV and Tuberculosis.

METHODOLOGY

The study is based on prospective collection of data of blood culture positive cases of gram negative bacteremia in patients who are admitted in medical ward and ICU in PSG hospitals. Details for the study will be recorded by interviewing

the patients or the family member of the patient who accompany them and also the current and past medical records of the patient. Patients with positive blood cultures for gram negative bacteria in medical ICU and medical wards will be reviewed daily and the clinical outcome is assessed based on MSOFA scoring (figure 1).

FIGURE 1: MSOFA SCORE

Modified Sequential Organ Failure Assessment (MSOFA) Score

Organ System	**0**	**1**	**2**	**3**	**4**
Respiratory SpO2/FiO2	>400	≤400	≤315	≤235	≤150
Liver	No scleral icterus or jaundice			Scleral icterus or jaundice	
Cardiovascular, hypotension	No hypo-tension	MAP <70 mm Hg	dopamine≤5 or dobutamine any dose	dopamine>5 epinephrine≤0.1 norepinephrine≤0.1	dopamine>15 epinephrine>0.1 norepinephrine>0.1
CNS, Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal, Creatinine mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0

MAP=mean arterial pressure

dopamine, dobutamine, epinephrine, and norepinephrine doses in micrograms per kilogram per minute

CNS=central nervous system

BLOOD CULTURE REPORTING SYSTEM

About 3-5 ml of blood is drawn from at least 2 different sites in BACTEC blood culture bottles under aseptic precautions and inoculated into culture medium and processed by semi-automated BACTEC system which gives a high yield of bacteria and also by disk diffusion technique. Antibiotic disks are used for antibiotic susceptibility testing along with automated VITEK system. All the reports are reported using standard published guidelines by CLSI (Clinical and Laboratory Standard Institute).

FIGURE 2 : ANTIBIOTIC DISKS PLACED ON AGAR SURFACE AFTER INOCULATION

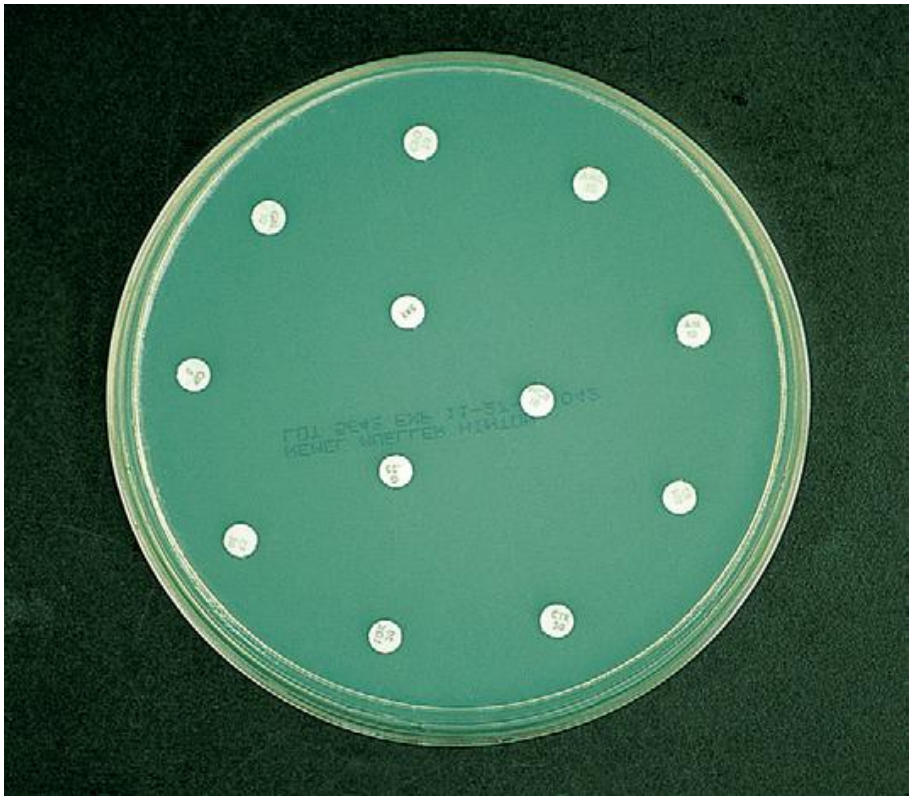


FIGURE 3: ZONE OF GROWTH INHIBITION AROUND DISKS AFTER INCUBATION

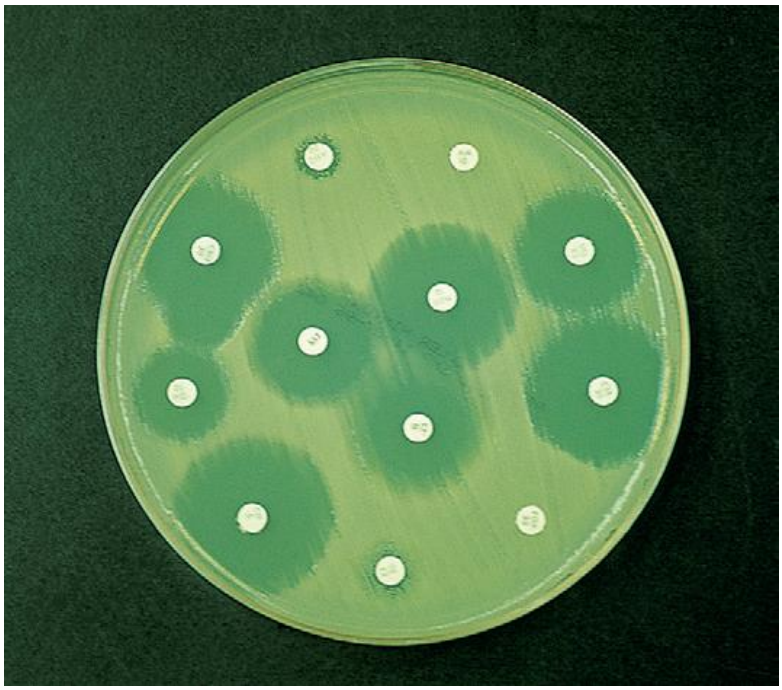


FIGURE 4: AUTOMATED VITEK SYSTEM

FIGURE 5: BLOOD CULTURE BOTTLES FOR BACTEC

FIGURE 6: AUTOMATED BACTEC BLOOD CULTURE SYSTEM

CASE DEFINITIONS

SEPSIS

As per 2001 consensus on sepsis it is defined as systemic inflammatory response syndrome with suspected or proven microbial cause . SIRS includes the presence of at least

2 of the following:

1. Temperature >38° C or <36°C,

2. RR >24/min or PaCO2 <32

3. HR > 90/min,

4. TC >12,000/l or <4000/l or >10% band forms

The study was carried out before the current changes in the sepsis definitions 2016 which defines sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection[8]

- Defined as an increase of 2 points or more in the Sequential Organ Failure Assessment (SOFA) score.
- In patients with infections, an increase of 2 SOFA points gives an overall mortality rate of 10%.

- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be quickly identified at the bedside with qSOFA (“HAT”); i.e. 2 or more :

    - Hypotension: SBP less than or equal to 100 mmHg
    - Altered mental status (GCS < 15)
    - Tachypnea: RR greater than or equal to 22

Gram-negative bacteremia is the identification of 1 or more gram negative bacteria from the patient on 1 or more occasions.

Appropriate empirical antimicrobial therapy was considered appropriate if the initial antibiotic selected should comprise at least 1 antibiotic that is sensitive in vitro against the disease causing bacteria that are followed with current medical standards.

Inappropriate initial antimicrobial therapy is the administration of an antibiotic to which the disease causing bacteria is resistant and if the antibiotic was not administered within 1 hour of clinical suspicion of sepsis.

Multi-drug resistant (MDR) gram-negative organisms: if the Organisms were susceptible to only one of the following antibiotic Classes: aminoglycosides, carbapenems, fluoroquinolones, penicillin or Cephalosporin.

STATISTICAL ANALYSIS

i. The data are reported as mean +/- SD or median depending on the distribution.

ii. Frequencies are expressed as percentage.

iii. The differences between quantitative variables between groups are compared by means of unpaired t tests.

iv. The chi square test are used to assess the difference in categorical variables between groups.

v. A p value of <0.05 using a two- tailed test was taken as being significant for all statistical tests.

vi. All data were analysed with statistical software SPSS, version 16.0 for windows.

REVIEW OF LITERATURE

GRAM NEGATIVE BACTERIA

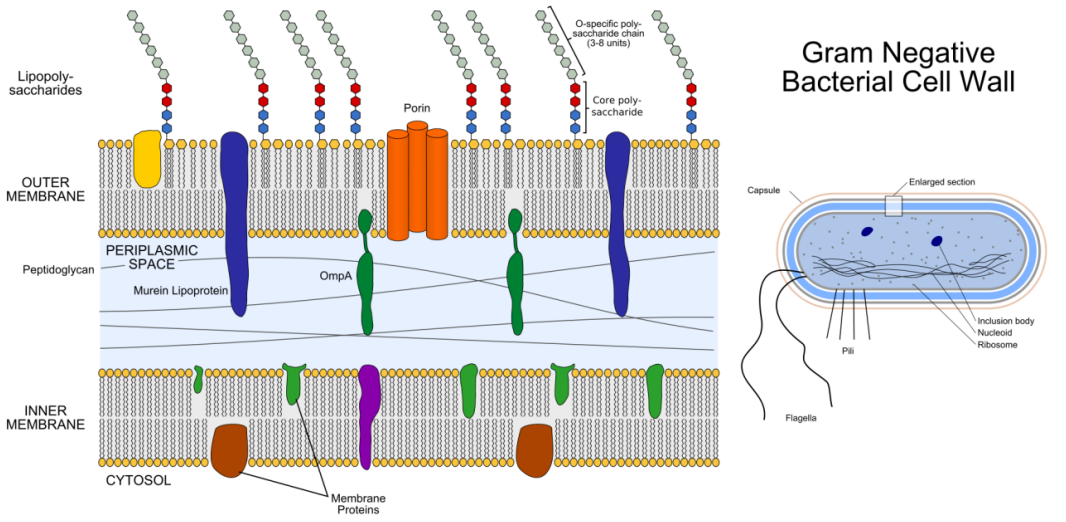


FIGURE 7: STRUCTURE OF GRAM NEGATIVE BACTERIA

COMMON GRAM NEGATIVE BACTERIA

Acinetobacter spp	Kingella spp
Actinobacillus spp	Klebsiella spp
Aggregatibacter spp	Legionella spp
Bartonella spp	Moraxella spp
Bordetella spp	Morganella spp
Brucella spp	Pantoea spp
Burkholderia spp	Pasteurella spp
Capnocytophaga spp	Proteus spp
Citrobacter spp	Providencia spp
Comamonas spp	Pseudomonas spp
Cronobacter spp	Ralstonia spp
Delftia spp	Raoultella spp
Eikenella spp	Salmonella spp
Enterobacter spp	Serratia spp
Escherichia spp	Shigella spp
Francisella spp	Stenotrophomonas spp
Haemophilus spp	Vibrio spp
Hafnia spp	Yersinia spp

INFECTIONS CAUSED BY GRAM NEGATIVE BACTERIA

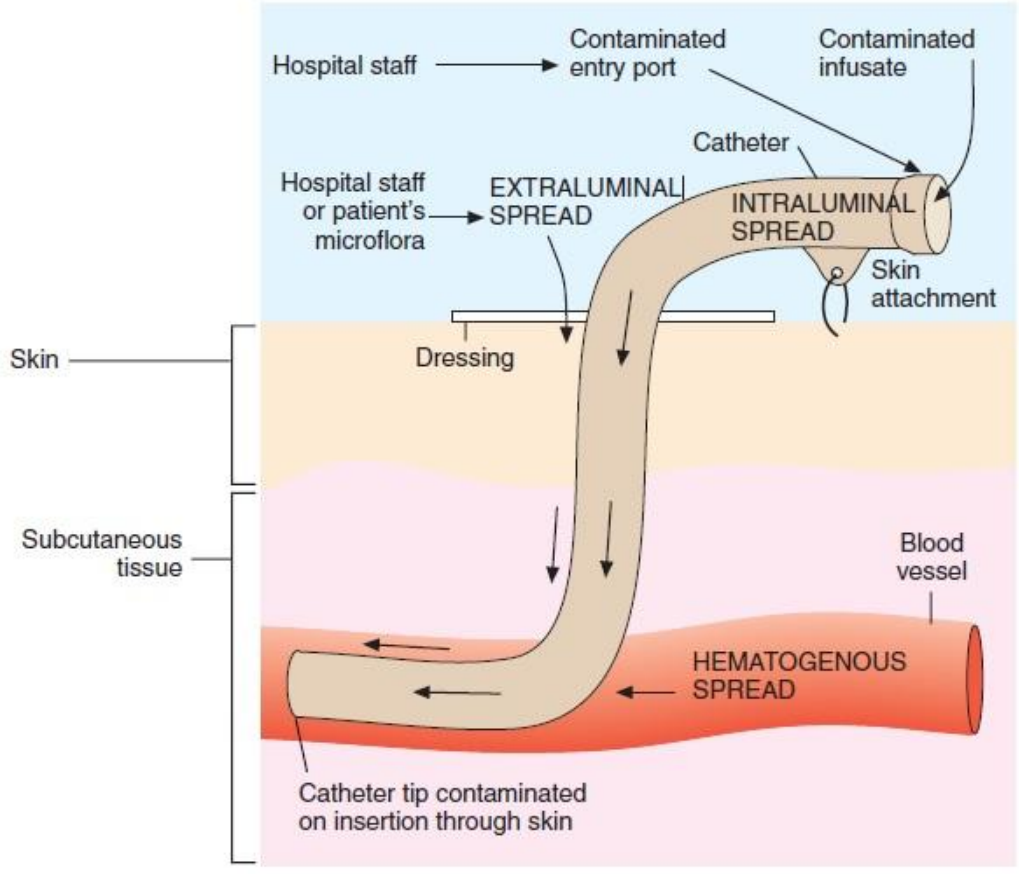
In the early 1940 majority of the infections were caused by Gram-positive bacteria. This lead to increased utility of the newly discovered penicillins and that lead to a worse clinical scenario of beta –lactam resistance to both gram negative and gram positive bacteria. As penicillins could no more be used as a single agent for infections cephalosporins came into play and they retained the properties of beta lactam drug for a certain period [7].

The most common beta-lactam antibiotic used to treat Gram-negative infections include extended-spectrum cephalosporin, penicillin-β-lactamase inhibitors and the carbapenems. Infection caused by gram negative bacteria ranges from uncomplicated community-acquired infections like otitis media, lower respiratory tract infections to severe ventilator-associated pneumonia. Oral beta lactams like amoxicillin and clavulanic acid and other cephalosporins like cefpodoxim, cefixime etc are used for community onset infections. Intravenous antibiotics like BLBLI and cephalosporins can be used for nosocomial infections . Carbapenems are often held in reserve to treat the serious infections caused by multidrug-resistant gram negative bacteremia Yet, continued prescription of these antibiotics for most of the serious infections has sustained the burden on many pathogenic bacteria to maintain enzymatic inactivation mechanisms that make penicillins fruitless in most of the critical situations. This pressure has caused in development of β-lactam resistance by inactivating enzymes, predominantly in Gram-negative organisms .

BLOOD STREAM INFECTIONS CAUSED BY GRAM NEGATIVE BACTERIA

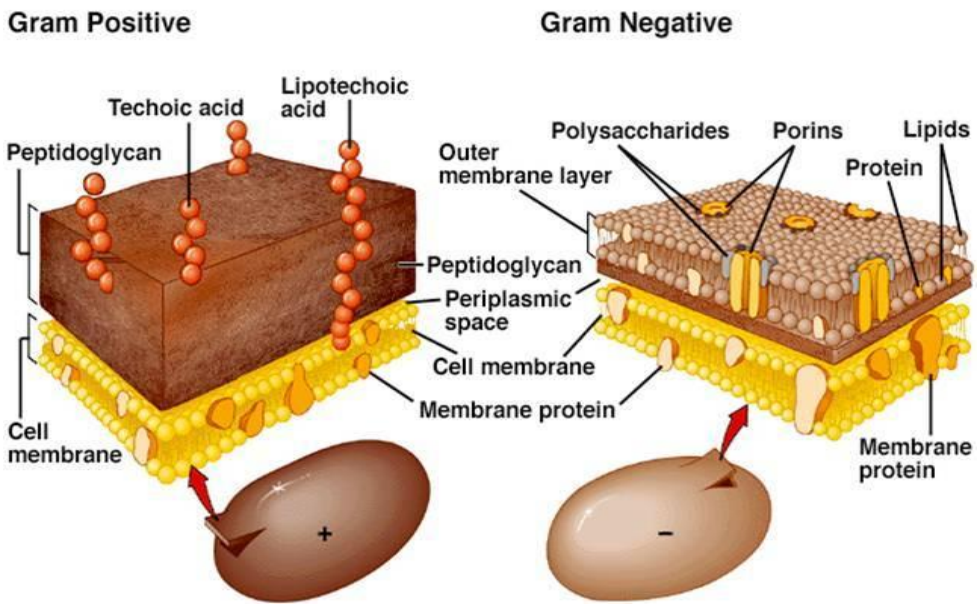
The 2 most common categories of bacteremia are intravascular and extravascular. Intravascular infection occurs due to spread of infection within the vascular system and they exhibit continuous bacteremia. The common causes are intravenous catheter related infections, infective endocarditis, suppurative thrombophlebitis and catheter related blood stream infections. The most common source of extravascular infections are genitourinary tract , wound site infection, biliary tract and respiratory tract [9].

FIGURE 8: PORTAL OF ENTRY OF BACTERIA



WHY GRAM NEGATIVE INFECTIONS ARE DIFFICULT TO TREAT

FIGURE 9: COMPARISON OF GRAM POSITIVE AND GRAM NEGATIVE BACTERIA



Gram negative bacteria are difficult to treat because of the following reasons

1. The outer membrane layer of the gram negative bacteria increases the toxicity in the host but gram positive bacteria do not possess this layer.
2. Antibiotics like penicillin are prevented from entry into the gram negative cells by the porin channels thereby causing treatment failure
3. The porin channels also expel the antibiotics hence making more difficulty in treating infections.
4. Gram negative bacteria possess both endo and exotoxins but gram positive organisms possess only exotoxins.

MECHANISM OF ANTIBIOTIC RESISTANCE

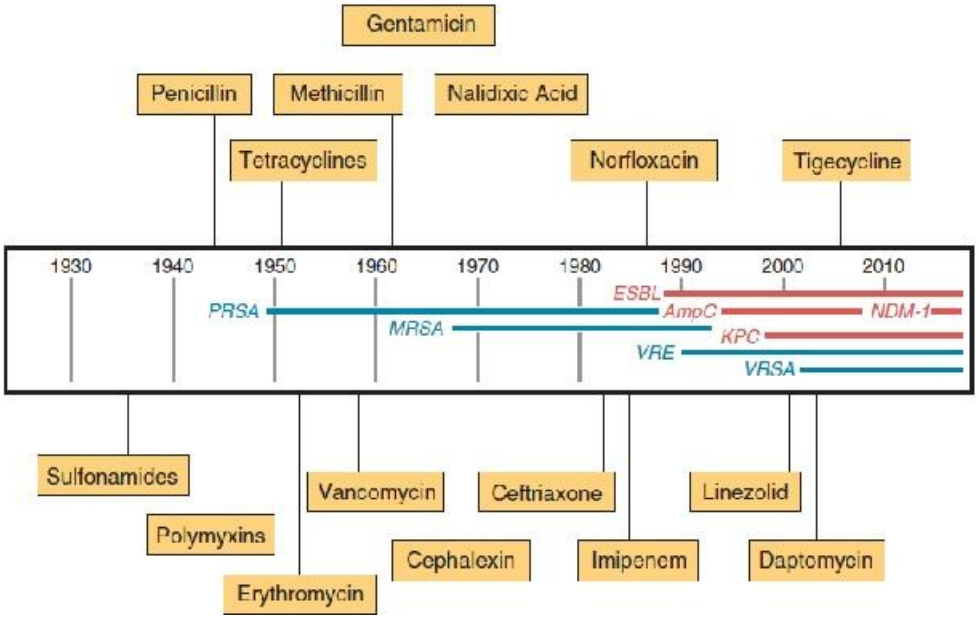


FIGURE 10: EMERGENCE OF ANTIBIOTIC RESISTANCE

The idea of antibiotic resistance emerged when they discovered an enzyme that was produced by a strain of E.coli destroyed the activity on penicillin. It was the same time when penicillin use was reported in the literatue. These antibiotics had the ability to cleave the beta lactam chemical bond, thereby disabling them in destroying disease causing bacteria [10].

CLASSIFICATION OF ANTIBIOTIC RESISTANCE IN GNB

Microorganism mediated antibiotic resistance can be classified as intrinsic resistance and acquired resistance [11, 12].

INTRINSIC RESISTANCE

This type of resistance is because of the normal anatomical , genitical or the physiological condition of the microorganisms. This type of resistance is inherited continuously among a particular bacterial species. This is helpful in identifying the resistant pattern of particular organism hence will be helpful in deciding which group of drugs could be used for sensitivity testing.

TABLE 1: RESISTANCE MECHANISMS OF GRAM NEGATIVE BACTERIA

NATURAL RESISTANCE	MECHANISMS
Gram-negative bacteria versus vancomycin	Lack of uptake resulting from inability of vancomycin to penetrate outer membrane.
P.aureginosa versus sulfonamides, trimethoprim, tetracycline.	Lack of uptake resulting from inability of antibiotics to achieve effective intracellular concentrations.
Klebsiella spp. versus Ampicillin	Production of Beta-lactamases destroy ampicillin before the drug can reach the protein binding site .
Enterococci versus Aminoglycosides	Lack of sufficient oxidative metabolism to drive uptake of aminoglycosides
Enterococci versus all Cephalosporin antibiotics	Lack of PBPs that effectively bind and are inhibited by these lactams.

ACQUIRED RESISTANCE

This is caused by altered cell genetics of the microorganisms. They are not inherited continuously and hence unpredictable. Hence different laboratory methods are required to detect various resistance patterns.

Over years about 890 types of beta lactamases have been identified in many of the bacterial specimens. There are almost 8 different mechanisms by which they exert the antibiotic resistance

1. Enzymatic inactivation.
2. Decreased permeability.
3. Efflux.
4. Alteration of target site.
5. Protection of target site.
6. Overproduce target.
7. Bypass of inhibited process.
8. Binding up of antibiotic.

RESISTANCE TO AMINOGLYCOSIDES

Resistance to Aminoglycosides is mediated by enzyme mediated or decreased uptake pathways. 3 types of enzyme modification occur in aminoglycoside antibiotics – phosphorylation, adenylation and acetylation. After modification of the aminoglycoside moiety its affinity for binding to 30S ribosomal subunit is diminished or completely lost. Aminoglycosides gain entry into gram negative bacteria through porin channels situated in the outer membrane. Hence, porin structure alteration also causes Aminoglycoside resistance.

RESISTANCE TO QUINOLONES

Resistance to quinolones occurs mainly by reduced intake or altered target. Gram negative bacteria prevents entry of quinolones into the cell's interior and also pumped out of the cell hence intracellular concentration of quinolones remains low to inhibit the DNA processing.

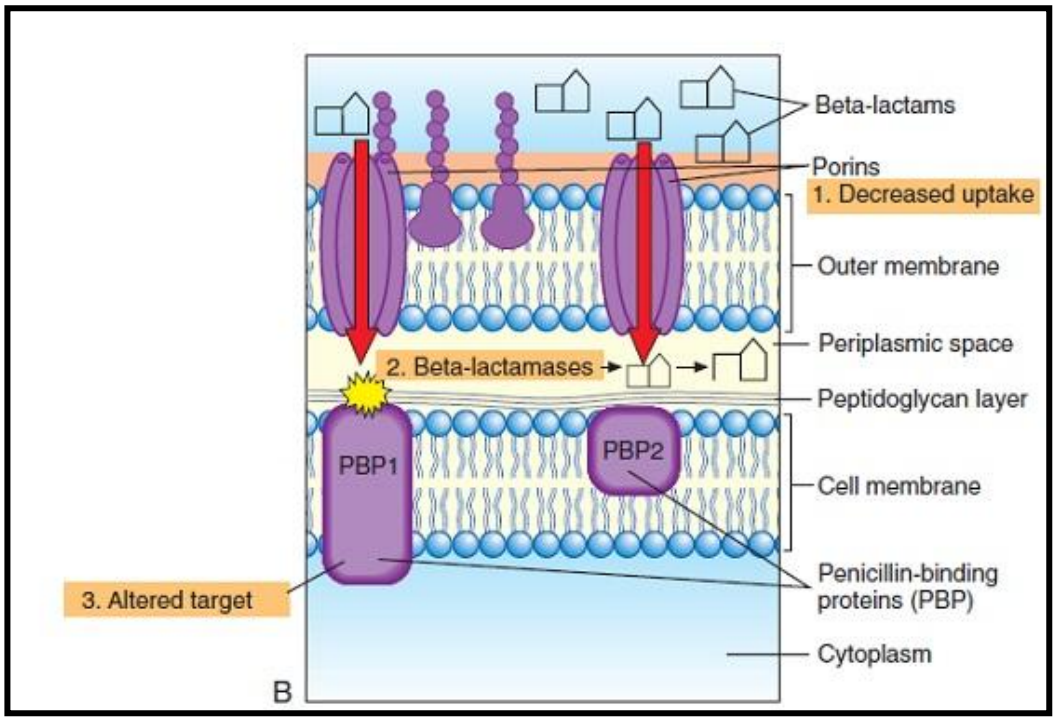
RESISTANCE TO BETA LACTAM ANTIBIOTICS

Resistance in beta lactam antibiotics occurs primarily by production of beta lactamases. These enzymes are encoded on genes located on the plasmids and when transposed they enable spread of multidrug resistance among multiple bacterias.

This is mediated by enzymatic destruction by the beta lactamases, which will lead to less affinity and less binding of antibiotics to the penicillin binding

protein sites [13]. This will also lead to efflux of antibiotics from the cell and reduced uptake of antibiotics .

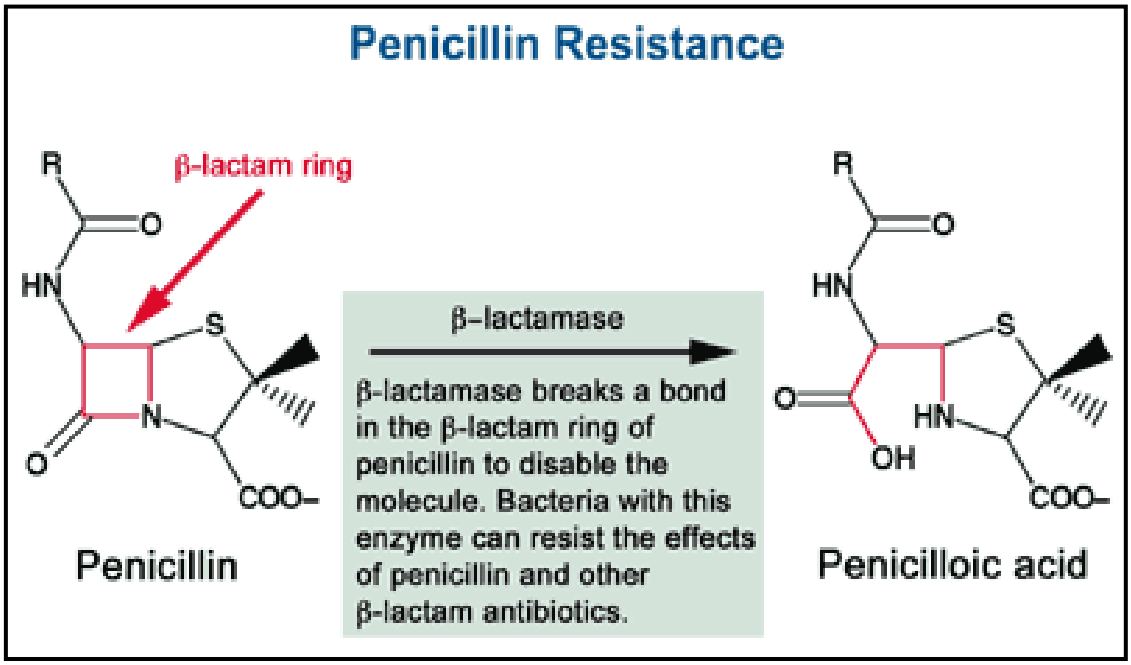
FIGURE 11: MECHANISM OF BETA LACTAM ANTIBIOTIC RESISTANCE



The beta lactamases open the beta lactam ring of the antibiotic and alter their structure leading to ineffective binding of antibiotic to the PBP. One important method to preserve the beta lactam ring is to combine two different beta lactam moieties so that one binds to beta lactamase and prevents hydrolysis in such a way that the second will exert its action. Some examples are Ampicillin/Sulbactam , Piperacillin / Tazobactam,

Amoxycillin /Clavulunate.

FIGURE 12: MECHANISM OF PENICILLIN RESISTANCE



With the development of penicillin resistance , cephalosporins emerged in the market but it was not so long when extended spectrum beta lactamases evolved and resistance to third generation cephalosporins developed and now emergence of carbapenamase has been widely reported [14].

Extended spectrum Beta Lactamase

1. **TEM -1** is the most common beta lactamase in gram negative bacilli and it can hydrolyse penicillins and narrow spectrum cephalosporins. These are most commonly seen in E.coli and Klebsiella spp.

2. **SHV – derived** beta lactamase are similar to TEM 1and found primarily in Klebsiella pneumonia strains due to point mutations.

3. **CTX-M derived** are acquired by plasmids from Ampc enzymes, these are also reported as most prevalent ESBL around the world.

4. **OXA – derived** are plasmid derived and are less inhibited by clavulanic acid. They are found mainly in P.aeruginosa and confer high level of resistance to oxymino beta lactams.

5. **AmpC enzymes** are the chromosomal enzymes that are resistant to beta lactamase inhibitors like clavulanic acid. There are more than 20 types of AmpC enzymes derived most commonly from Klebsiella and Enterobacter spp.

6. **Carbapenamases** are the largest group of antibiotic resiatance because they are resistant not only to broad spectrum penicillins , cephalosporins but also to carbapenems.

7. **Class B metallo – betalactamases (MBL)** causes hydrolysis of the beta lactam ring by zinc cation and they are reistant to sulbactum , tazobactam and clavulunate except monobactams.

8. **New Delhi Metallo Beta Lactamase -1 (NDM - 1)** was discovered in 2008 in India in a Klebsiella isolate and then it has been reported in US and UK. They are resistant to all beta lactams and aztreonam is the exception [15].

PREVALENCE OF GRAM NEGATIVE BACTERAEMIA

Studies have reported the prevalence BSI caused by gram negative organisms were 22.5% with E.coli , 14% by other gram negative organisms like Klebsiella spp , enterobacter spp, Pseudomonas spp.

Among ICU patients, the rate of gram-negative BSI caused by P. aeruginosa were higher. Patients in the ICU are exposed to more antibiotics antibiotics, hence there is an increase in the risk of infections with by P. aeruginosa and Acinetobacter species, which have acquired or intrinsic resistance to most of the commonly used antibiotics .In a study among 45 cases of hospital-onset BSI in an ICU in US, the following distribution was noted [16]:

- Enterobacter spp. – 22.2%
- K. pneumoniae – 17.8%
- E. coli – 15.6%

A study of 306 cases of community-onset , health care-associated gram-negative bloodstream infections demonstrated the following infection rates. [17]. These patients had significant health care exposures and the distribution of organisms causing bacteremia in such patients reflects a hybrid between the hospital acquired or community acquired distributions.

- E. coli – 47.4%
- K. pneumoniae – 14.7%
- P. aeruginosa – 9.2%
- Enterobacter species – 6.5%

A study in a tertiary care hospital in South India has reported 77.86% of the bacteremia was caused by E.coli and 22.14% by Klebsiella spp [18].

A study conducted in a tertiary care hospital in India between 2011-2012 for identifying the prevalence of various infections found that Gram-negative organisms were the most common cause [19]. The rate of infection are the following

- K. pneumonia- *18.7%*
- E. coli- *21.0%*
- Pseudomonas aeruginosa -14.0%.

RISK FACTORS

In a study of 326 patients with gram-negative bacteremia, comorbid conditions were identified in 315 (97 percent) [20]. Conditions identified in this and other studies included [21]:

- Hematopoietic stem cell transplant .
- Liver failure.

- Solid organ transplant.
- Diabetes Mellitus.
- Lung disease.
- Chronic kidney disease .
- HIV / AIDS .
- Glucocorticoid therapy.

EMPIRICAL ANTIBIOTIC IN GRAM NEGATIVE SEPTICEMIA

No RCT are available till date to evaluate the empirical antibiotic of choice suspected gram-negative bacteremia but many trials have evaluated for treatment of sepsis and septic shock , which included bacteremia due to both gram negative and gram-positive organisms and also other non bacteraemic causes.

National Treatment Guidelines for Antimicrobial Use in Infectious Diseases by Directorate General of Health Services Ministry of Health & Family Welfare Government of India has formulated the new guidelines in 2016 for empirical antibiotic therapy [22]. Some of them are listed below.

TABLE 2: INDIAN GUIDELINES ON EMPIRICAL ANTIBIOTIC THERAPY

DISEASE	MOST COMMON PATHOGEN	EMPIRICAL ANTIBIOTIC OF CHOICE
Community acquired pneumonia	S.pneumoniae, H.influenzae, Legionella, E.coli, Klebsiella sp., S.aureus	Mild to moderate cases 1.Amoxycillin- 500mg-1 g TDS oral. If IV indicated, amoxicillin clavulanate 1.2 g IV TDS or 2.Ceftriaxone 2g IV OD For Severe cases 1.Amoxycillinclavulanate 1.2 g IV TDS Or Ceftriaxone 2g IV OD Duration 5-8 day Azithromycin 500 mg or doxycycline if atypical organisms suspected

Biliary tract infections (cholangitis, cholecystitis)	Enterobacteriaceae (E.coli, Klebsiella sp.)	Ceftriaxone 2gm IV OD or Piperacillin / Tazobactam 4.5gm IV 6 hourly or Cefoperazone / Sulbactam 3gm IV 12hourly For 7-10 days
Secondary peritonitis, Intra-abdominal abscess/ GI perforation	Enterobacteriaceae (E.coli, Klebsiella sp.), Bacteroides(colonic perforation), Anaerobes	Piperacillin / Tazobactam 4.5gm IV 6 hourly or Cefoperazone / Sulbactam 3gm IV 12 hourly in severe infections In very sick patients, if required, addition of cover for yeast (fluconazole iv 800 mg loading dose day 1, followed by 400 mg
Complicated Pyelonephritis	Escherichia coli, K.pneumonia, Proteus mirabilis, P.aeruginosa, Enterococcus sp.	Piperacillin Tazobactam 4.5gm IV 6 hourly or Amikacin 1 g OD IV or Cefoperazone Sulbactam 3gm IV 12 hourly
Enteric fever	S.typhi, S.paratyphi A	Outpatients: Cefixime 20mg/kg/day for 14 days or Azithromycin 500 mg BD for 7 days. Inpatients: Ceftriaxone 2 g IV BD for 2 weeks +/-Azithromycin 500 mg BD for 7 days

The below one is the guidelines followed by John Hopkins University for MDR gram negative bacterial infections.

JOHN HOPKINS GUIDELINES ON TREATMENT OF MDR GRAM NEGATIVE BACTERIA [23]

ESBL PRODUCERS :

1. Meropenem 1 gm Q8H for all severe infections if organisms are susceptible.
2. Ertapenem 2gm Q24H for uncomplicated UTI and soft tissue infections when adequate source reduction is done and organism is susceptible.

CARBAPENAMSE PRODUCERS:

1. Meropenem 2 gm Q8H infused over 3 hours for all infections. This is based on retrospective studies showing significant benefits in clinical outcome even when the organism is intermediate or resistant PLUS other agents like Tigecycline, Amikacin, Colistin should be added except for urinary tract infections.

MDR GRAM NEGATIVE PATHOGENS:

Organisms are said to be MDR if they are susceptible to only one group of antibitics which includes carbapenems, cephalosporins, penicillins, fluroquinilones or aminoglycosides.

MULTIDRUG REISTANT PSEUDOMONAS

Anti-pseudomonal beta lactam with a aminoglycoside with synergy is suspected or if synergy is present.

MULTIDRUG REISTANT ACINETOBACTER

Beta lactam antibiotic plus aminoglycoside or Ampicillin/Sulbactam plus Aminoglycoside or Tigecyclin / colistin.

TIMING OF ANTIBIOTICS

The Surviving Sepsis Campaign (SSC) laid by The Society of Critical Care Medicine (SCCM) and The European Society of Intensive Care Medicine(ECCM) on the management of sepsis and septic shock in 2012 has concluded the following measures are to be undertaken during early hours of sepsis management [20]. It includes

1. Administration of effective IV antibiotic within the 1 hour of recognition of severe sepsis without septic shock and in septic shock
2. In neutropenic patients with severe sepsis a combination empirical antibiotic therapy is recommended and same is for patients with difficult-to-treat, MDR bacteria such as Pseudomonas spp A.baumannii.
3. In suspected Pseudomonas bacteremia in patients with severe infections with septic shock and respiratory failure, the recommendation is a

combination therapy with an extended spectrum beta-lactam and either a fluoroquinolone or an aminoglycoside.

This study also evaluates the timing and appropriateness of empirical antibiotic therapy on the clinical outcome of gram negative bacteremia considering the importance of the early golden hours in management of sepsis.

STUDIES ON EPIDEMIOLOGY OF GRAM NEGATIVE BACTEREMIA

The trend of blood stream infections has been changing over years , study by Wilson et al assessed the changes in trend of pathogens causing bacteremia in England between 2004 and 2008 , the study reported 97,195 cases of blood stream infections and more than half of the infections occurred in elderly age group >65 years of age . 54% of the infection occurred in males. The study has reported 12 most common pathogens causing infection and of which E.coli was the most frequent organism encountered. It accounted to 22.5% of all the infections. Infection caused by other gram negative organisms like klebsiella spp., Pseudomonas spp., Enterobacter spp., and protease accounted to about 14% of the infections. In a period of 5 years there has been an increase in percentage of E.coli infection in elderly age group. The rate of bacteremia increased from 23% to 30.5%. The study also reported an increase in rate of infection caused by other gram negative organisms. Infection caused by Klebsiella spp., increased by 14% , Protease spp., by 13% ., Pseudomonas spp., by 24% [1].

From the above data it is clear that there has been a sharp rise in the rate of bacteremia caused by E.coli. E.coli has contributed to almost half of the 12 most common reported organism. Recent study has also shown that E.coli isolates were resistant to cephalosporins like cefotoxime and ceftazidime. The resistant rate was 2% in 2001 and 12% in 2006. The most common source of bacteremia was urinary tract infection, respiratory tract and intravenous devices. Bacteria caused by Klebsiella spp., and pseudomonas spp., were mostly hospital acquired.

Study by Al Hasan et al., focused on blood stream infections caused by gram negative bacteria in a 10 year population based cohort study found that E.coli accounted to 54% of the infections and Klebsiella spp., Pseudomonas spp., Enterobacter spp., proteus spp., were 12.1% , 6.5%, 2.8%, 3% respectively. The study also analysed the recurrence of BSI caused by these organisms and found that E.coli was the most common organism reported and the incidence rate was 52%. The most common source of bacteremia was urinary tract in almost 57% of the patients followed by gastrointestinal tract(11.5%) , respiratory tract(7.6%) , skin and soft tissue(2.5%) and central venous line related (1.9%). The primary source was unknown in 18,6% of the patients. The study has also calculated that 50.5% of the infections were community acquired and 36.2% were healthcare associated and 13.4% were nosocomial infections [17].

A prospective study in a tertiary care hospital in south India which analyzed the epidemiology of bacteremia caused by ESBL – producing E.coli and Klebsiella spp. found that 77.8% of the bacteremic episodes were caused by E.coli and 22.14 % of the episodes by Klebsiella spp. Urinary tract infection was the primary source of bacteremia in 45% of the patients. This study shows an unusually increased prevalence of ESBL infection in a Indian tertiary hospital [18].

Another original research article published in south India in 2014 has reported about 11.6% of gram negative blood stream infections.

STUDIES ON TREATMENT OF GRAM NEGATIVE BACTEREMIA

The first step in treatment of any infection is choosing an appropriate antibiotic therapy. The clinician has to choose between a broad or narrow spectrum antibiotic because a broad spectrum antibiotic may result in increased cost and increases rate of adverse events whereas a narrow spectrum antibiotic may lead to treatment failure and death.

A study by Tehrani et al. analyzed on the choice of empirical antibiotic in gram negative septicemia. The study concluded that in patients presenting with septic shock a beta lactam antibiotic with antipseudomonal activity would be an ideal choice as the death rate is high if antibiotic is not quickly and adequately delivered, particularly in Pseudomonas bacterial infection. For patients without septic shock use of a combination of aminoglycoside and beta lactams were suggested. [4]

A prospective observational study by Leibovici et al. analyzed on monotherapy versus combination therapy for treatment of gram- negative blood stream infections. The study compared both empirical and definitive treatment with combination treatment versus beta lactam antibiotic and aminoglycoside versus single beta lactam antibiotic. Patient treated with a single aminoglycoside worsened faster when compared to patients treated with a beta lactam antibiotic. The only exception was bacteremic urinary tract infection which had a better prognosis than those caused from other sources[3]. One possible explanation would be the preferential concentration of aminoglicosides in the kidneys.

A study by Tamma et al. the study mainly focused on beta lactam monotherapy versus beta lactam and aminoglycoside or fluroquinolone combination therapy. The selection of empirical combination therapy for suspected infections with Gram-negative bacteria should to be made after analyzing the local epidemiology and patient characteristics. Prior to prescribing antimicrobial therapy, resistance patterns within an institution are important to consider [25].

When resistance to beta-lactam antibiotic is suspected in patients with sepsis secondary to Gram-negative bacteria, the addition of an aminoglycoside antibiotic until antimicrobial susceptibility pattern are known appears to be justified. For infections with Gram-negative organisms, antimicrobial synergy

has been seen with beta-lactam antibiotic and aminoglycoside combinations. [21].

A review by Chow et al., on combinations versus monotherapy for gram negative bacteraemia has concluded that the indications for combination antibiotic therapy should be confined to immunosuppressed patients, patients with suspected Pseudomonas aeruginosa , Klebsiella pneumonia infections and severely ill patients assessed by APACHE score or Pitt bacteremia score. On the other hand monotherapy would be sufficient in many of the clinical situations like infections caused by less virulent organisms like E.coli , urinary tract associated bacteremia , immunocompetent individuals with stable vital signs and normal mental status without signs of septic shock. Eventhough these patient may be prone to higher mortality rates, this may be due to longer hospital stay and disease complications rather than antibiotic resistance or virulence of bacteria.[26]

An analysis by kollef et al. on the use of broad spectrum antibiotics in serious blood stream infections analyzed that in patients with ESBL producing E.coli or K.pneumoniae bacteremia the 30 day mortality rates were lowest among those who had received a carbapenem antibiotic(12.9%). In another prospective study involving 43 patients with bacteremia caused by ESBL producing E.coli, the mortality rate was 9% in those who had received a beta lactam/ beta lactamase inhibitor or a carbapenem antibiotic. The mortality rate was 35% in those who had received a fluroquinolone or cephalosporins.

Changes in antibiotic therapy was required in only 24% of the patients who were started on empirical beta lactam/ beta lactamase inhibitor. Whereas the change in antibiotic rate was 78% in those who have received a cephalosporin group [27].

A retrospective evaluation of 54 patients with bacteremia caused by organisms other than E.coli and Klebsiella spp. found that there is no significant change in mortality rates with ciprofloxacin and carbapenems which was 70% and 72% respectively.

A prospective observational study which analyzed outcome of antibiotic combination therapy versus monotherapy in 230 patients with Klebsiella bacteremia found no statistical difference in mortality between 118 who received monotherapy and the remaining 112 patients who received a beta lactam and an aminoglycoside. The mortality rate was 20% in the earlier group and 18% in the latter group. But in patients who had hypotension within 72 hours on the day of positive blood culture or prior showed a significantly lower mortality rate of 24% when received a combination antibiotic as compared to those who received a monotherapy which was 50% [28].

A prospective study in a tertiary care hospital in south India which analyzed the outcome of bacteremia caused by ESBL producing E.coli and Klebsiella Spp. had found higher rate of resistance to beta lactamand beta – lactamase inhibitor (67.2-81.7%). Resistance to third generation cephalosporin was 73.3% and fluoroquinolones (73.3%). Carbapenems were the most active

antibiotic among all others tested. It was concluded in the study to initiate carbapenems as the initial antibiotic of choice for serious infections and de-escalation after the culture reports are available [29].

A systemic review and meta- analysis by Shiber et al. which included 31 RCT analyzed on the difference in outcome comparing BLBLIs and carbapenems, found that there was no significant difference in outcome both in terms of clinical and microbiological aspects. The study found that all-cause mortality after 30 days or during follow-up showed no difference between the BLBLI and carbapenem group but the study did not have data on the ESBL producing organisms and the impact of BLBLI and carbapenems on outcome [30].

A prospective observational study by Paterson et al. compared the efficacy of different antibiotcs used in K. pneumoniae bacteremia caused by ESBL producers. The study found that carbapenems had a lower incidence of 14 day all- cause mortality rates compared to other antibiotics. The patients who had received a carbapenem either as monotherapy or combination therapy after culture positivity for K.pneumoniae had mortality of 4.8% which was significantly lower compared to those who did not receive a carbapenem(27.6%). The study showed 100% in vitro susceptibility of klebsiella to imipenem.47% were resistant to piperacillin/ Tazobactam. Lower outcome to other antibiotics was thought to be because of inoculum effect [31].

A study by vasilev et al. on tigecycline in the selected serious infection with resistant gram negative bacteria including Klebsiella pneumonia Enterobacter spp and Acinetobacter baumannii showed that clinical cure rate was 72.2% and microbiological eradication rate was 66.7% with tigecycline. Data has shown that tigecycline activity was not affected by ESBL production and even the MIC was low (2 mg/l) when compared to other antibiotics used for ESBL producing Klebsiella pneumonia. Tigecycline had an in vitro activity of >90% against ESBL producers. It was concluded in the study that tigecycline is a safe and efficacious drug in treatment of multi drug resistant gram negative bacterial infections [32].

A study on combination therapy of antibiotics for gram negative bacterial infections caused by multidrug resistant organisms has suggested a combination therapy with broad spectrum beta lactam and a fluroquinolone or aminoglycoside in severe sepsis and infections caused by Pseudomonas spp. For infections caused by multidrug resistant Acinetobacter spp. combination therapy that includes ampicillin/sulbactam, aminoglycoside , carbapenem or colistin was successful. Colistin , by its detergent mechanism increases the outer membrane permeability enabling other antibiotics to exert its action. Thus addition of rifampin to meropenem/doripenem and colistin caused synergistic effects in vitro against MDR Pseudomonas spp. Carbapenamase producing Enterobacteriaceae , Acinetobacter spp [33].

A study by Michalopoulos et al. studied the clinical outcome with colistin treatment in ICU acquired infection caused by A.baumani or P.aeruginosa that was sensitive only to colistin. Concomitant antibiotic therapy was carbapenem and ampicillin – sulbactam. Clinical cure was observed in 69.8% of the patients. Hence further studies are required in analyzing the efficacy of colistin with other synergistic antibiotics in the current scenario of multidrug resistant organisms [34].

A systemic review and meta- analysis was done by Vardakas et al. analyzed 21 studies that compared the efficacy of carbapenems and non-carbapenems. The study did not show any statistical difference in mortality between carbapenems and BLBLIs. But the study has many limitations most of the patients who had received BLBLI had also received carbapenems at some point of the treatment as combination therapy. The second limitation was the study included only ESBL producing Enterobacteriaceae. The study did not report on the outcome depending on dose and duration of antibiotics. Other limitation was the study included all sources of bacteremia like nosocomial, community acquired and healthcare associated infections; it is common that many of the variables would not be common in all the groups. Lastly publication bias was also detected in funnel plots [35].

A study by Tamma et al on carbapenem therapy for ESBL producing bacteria found that carbapenems were associated with lesser mortality compared to Piperacillin/Tazobactam group. The mortality rate was 8% among

the carbapenem group and 17% in the Piperacillin/Tazobactam(PTZ) group. The study concluded that carbapenems can be used as a empirical antibiotic of choice in ESBL suspected infections after considering previous hospitalization, prolonged ICU stay and immunocompromised state etc [36].

STUDIES ON ANTIBIOTIC SUSCEPTIBILITY OF GRAM NEGATIVES

In a retrospective study done in Indonesia in 2009 on antibiotic susceptibility found that P. aeruginosa showed high rate of resistance to cephalexin (96%) cefotaxime 65%. The most sensitive antibiotic was Amikacin which was 84% sensitive followed by imipenem which was 81% sensitive. The study also analyzed the antibiotic susceptibility pattern of K. pneumonia and found that high degree of resistance was seen in the cephalosporin group with 86% to cephalexin and 75% to ceftriaxone [37] .

A retrospective study done in a tertiary care hospital in South India found high prevalence of E. coli (36.5%) followed in order by 19% of klebsiella species and 18.7% by pseudomonas group. Acinetobacter species contributed to 12% of the total gram negative isolates. The sensitivity pattern were 87% sensitive to Amikacin , 79% sensitive to Piperacillin Tazobactum, 58% sensitive to cefoperazone sulbactum , 78% sensitive to Imipenem. Among Klebsiella species maximum sensitivity was with Piperacillin Tazobactum which was around 80% followed by Imipenem , Amikacin , Cefoperazone sulbactum whose sensitivity was 76% , 68% , 44% respectively.

Among Pseudomonas species Amikacin was the most sensitive antibiotic whose sensitivity was 93.7%. almost 100% of the Enterobacter species was sensitive to piperacillin Tazobactum [38].

A retrospective study done in India found a high level of resistance of gram negative bacteria to cephalosporins (70%) and beta lactams (more than 65%). Almost 52% of the gram negative E.coli were ESBL producers. 5% of the ESBL producers were resistant to carbapenems. Acinetobacter species showed high level of resistance to imipenem and meropenem which was 97% and 82% respectively. The study also reported high sensitivity of E.coli to carbapenems (94%) followed by BLBLI (80%) but showed low sensitivity to fluroquinolones(80%). The resistance to carbapenems were only 3-5% [39].

A research article published in 2014 on antibiotic susceptibility of various bacterial isolates found that E.coli was the most common organism among the gram negatives and it was isolated in 32.6% of the total gram negative bacterial isolates, Klebsiella spp. contributed to 25% , Pseudomonas(9%) and Acinetobacter (13%). Almost all the gram negatives showed nil resistance to imipenem. Among E.coli 73% were resistant to Amoxycillin/Clavulanic acid, 85% were resistant to ceftriaxone, 75% were resistant to piperacillin / Tazobactam. Among Klebsiella spp 90% were resistant to Amoxycillin/Clavulanic acid 68% were resistant to ceftriaxone , 66% were resistant to Amikacin and 50% resistant to piperacillin / Tazobactam.

Among Acintobacter spp. 85% were resistant to ceftazidime 57% were resistant to Amikacin, 66% to piperacillin / Tazobactam [40].

Singh et al. in their study found that Enterobacteriaceae were resistant to ampicillin in 91% of the isolates, 86% to amoxicillin/ clavulanic acid, 88% of the isolates were resistant to ceftriaxone. Lesser resistance rate was reported among imipenem (0.93%). Acinetobacter showed 50% resistance to aminoglycosides, 20% to Piperacillin /Tazobactam and 75 to Imipenem. Pseudomonas were 100% responsive to imipenem and 7% resistant to to piperacillin / Tazobactam [41].

A retrospective study on antibiotic susceptibility of various gram positive and gram negative bacteria found that E.coli was 86% sensitive to aminoglycosides and 76% sensitive to BLBLI. Acintobacter spp was 90% sensitive to cefoperazone/sulbactam and 76% sensitive to aminoglycosides. 70% of the klebsiella were sensitive to piperacillin/tazobactam and 66% to Amikacin. Almost all the Pseudomonas isolated were sensitive to Amikacin, 53% of then were sensitive to piperacillin/tazobactam.

Of the gram negative bacilli, Acinetobacter baumannii was resistant to cephotaxime (90%) , Aminoglycosides (76.19%) . E. coli was highly resistant to Ampicillin (70%), Piperacillin/Tazobactum (26%), Cefoperazone/Sulbactum (15%); Imepenem (19.6%), Klebsiella spp. was resistant to cephotaxime (70%) , ciprofloxacin (62.5%), Cefoperazone/Sulbactum (29.1%); Pseudomonas was resistant to ampicillin (60%), amikacin (20%) [42] .

STUDIES ON APPROPRIATE EMPIRICAL ANTIBIOTIC THERAPY

MONARCS trial which was a RCT included 2634 patients with suspected sepsis found that adequate antibiotic therapy was given in 91% of the patients and the mortality rate for patient who received adequate antibiotic therapy was 33% and in patients who received inappropriate antibiotic therapy the mortality rate was 43%. The study has concluded that the overall mortality rate reduction was 10 % when adequate empirical antibiotic was prescribed. An exception in that study was the mortality rate did not improve for a group of patients with Pseudomonas infection even if antibiotic therapy was appropriate. One another significant finding was that even in patients with clinical signs associated with higher mortality rates and severe sepsis there was a significant reduction in mortality rates when empirical antibiotic of choice was appropriate [43].

In a study by Leibovici et al. which included 2165 patients with gram negative bacteremia found that 670 of the patients were given inappropriate empirical antibiotic therapy and the mortality rate was 34% and mortality rate was 18% in those population who received adequate antibiotic therapy. Another study by the same researchers on analysis of risk factors and outcome of sepsis identified that in patients with septic shock and bacteremia the mortality rate was 75% when an appropriate antibiotic was chosen empirically and the mortality rate increased to 85% when an inappropriate antibiotic was opted [44].

Most of the studies which have analyzed the effect of appropriate antibiotics on clinical outcome like mortality has found at least a 10% reduction in mortality rates when antibiotic was appropriate.

A research article by Behrendt et al. in 2013 analyzed the influence of antibiotic therapy on outcome in patients with culture positivity. They have concluded from the study that the mortality was 15.9% in patients who had received appropriate antibiotic empirical therapy and 28.8% for the inappropriate empirical antibiotic group of patients. The study also compared the time to administration of antibiotic and its impact on mortality. It was found that in patients started on antibiotic with 48 hours had a mortality of 15% as compared to 31% in patients receiving antibiotic after 48 hours [45].

A retrospective cohort study among 2731 patients admitted in ICU with septic shock was done by Kumar et al. The study analyzed on the effect of time interval of antibiotic administration and its relation with survival. The study showed makeable increase in mortality of 7.5% for every hour of delay in administration of antibiotic. When comparing the antibiotic administration within 1 hour to 6 hours of suspected sepsis the survival rate drastically decreased from 80% to 44%. The study also highlighted a significant delay in antibiotic administration in 30% of the patients who had not received antibiotics even after 12 hours. Only 14% of the patients received antibiotics within 1 hour of suspicion of sepsis [46].

A systemic review and meta-Analysis which included 70 prospective studies for the analysis showed that mortality was substantially higher in all the sub groups with inappropriate empirical antibiotic therapy even after adjusting for all the confounding variables. The study demonstrated a large benefit of appropriate antibiotic in patients presenting with septic shock as evidenced by high odds ratio. Other variables like age , source of bacteremia , causative agent , presence or absence of neutropenia did not affect the results. The study finally concluded that all-cause mortality was considerably associated with empirical antibiotic was not appropriate [47].

A study by Joo et al. which analyzed the outcome in P.aeruginosa based on the empirical antibitotic initiation retrospectively in 202 patients, 39.6% of the patients had been given inappropriate antibiotic empirically. The study found that the impact of antibiotic therapy depends on the source of infection. In High risk sources of infection like intra- abdominal and lung , inappropriate antibiotic was independently associated with mortality. But it was not significantly associated in overall mortality. The study suggested the use of broad spectrum anti- pseudomonal coverage in high risk sources of infection whenever suspected [48].

A prospective study by Zaragoza et al. which included 3225 eligible patients with bacteremia in 166 ICU found that 23.5% of the patients received an inadequate empirical antibiotic therapy. 11% of the patients with septic shock did not receive an appropriate antibiotic therapy. The most common

GNB isolated was A.baumannii. Among patients who received inappropriate empirical therapy, gram negative organisms were isolated in nearly 54% of the patients. The study did not show a significant association between outcome and appropriateness of antibiotic therapy [49].

Harbarth et al. in his study on effect of initial antibiotic of choice and clinical outcome among patients enrolled in a clinical trial for immunomodulation therapy with documented sepsis found that among 23% of the inappropriate antibiotic group the mortality was 39% when compared to the appropriately treated group where the mortality was 24%. After adjusting for the variables that could affect the mortality like age , comorbid illness, malignancy , liver disease , liver disease , renal failure etc it was found that there was an independent association between inappropriate antibiotic therapy and increased fatality [50].

STUDY ON VALIDATION OF MSOFA SCORING

A retrospective analysis of a prospective observational study was done 1770 patients. The MSOFA and SOFA was sequentially analyzed for all the patients.

The main objective of the study was to predict the requirement of invasive ventilation and also to predict the risk of mortality following admission. Though SOFA is a validated scoring system for predicting mortality there are many technical difficulties faced because of many laboratory parameters involved such as respiratory, hematological , renal and liver. This

could be less feasible in a resource limited settings but MSOFA eliminates many of the lab parameters like platelet count, PaO2 is replaced by Spo2/Fio2 ratio. Serum bilirubin is replaced by assessment of icterus clinically. The only lab parameter used is serum creatinine. The cardiovascular, nervous system and renal scores are same for both SOFA and MSOFA. Hematological score was excluded in MSOFA. MSOFA is a 5 system scoring from 0-4, with the maximum score of 19. The end points for validation were need for invasive ventilation on day 3 and day 5 and 30- day mortality. It was concluded from the study that there was no difference between MSOFA and SOFA in predicting mortality [51 , 52].

A observational cohort study on ICU patients compared the efficacy of SOFA, APACHE II and MSOFA in predicting outcome found that MSOFA and SOFA are efficacious than APACHE II in predicting clinical outcome [53].

RESULTS

Among the 60 patients included in the study more number of persons was in between the age group of 61 years to 70 years (Table 3) and they constituted to 23% of the total study population, followed by 51-60 years who contributed to 18% of the study people (Figure 13).

TABLE 3: AGE DISTRIBUTION OF GRAM NEGATIVE BACTEREMIA

Age Distribution			
	Gender		
Age	Male	Female	Total
<40	2	3	5
41 – 50	3	3	6
51 – 60	8	10	18
61 – 70	7	14	21
>70	5	5	10
Total	25	35	60

FIGURE 13: GRAPHICAL DEMONSTATION OF AGE DISTRIBUTION

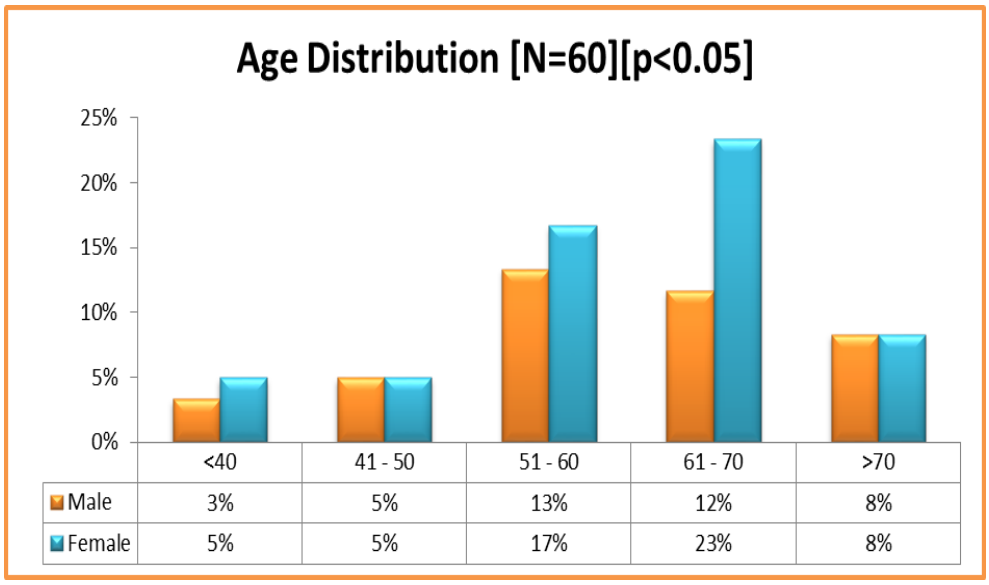


FIGURE 14: PERCENTAGE DISTRIBUTION OF GENDER

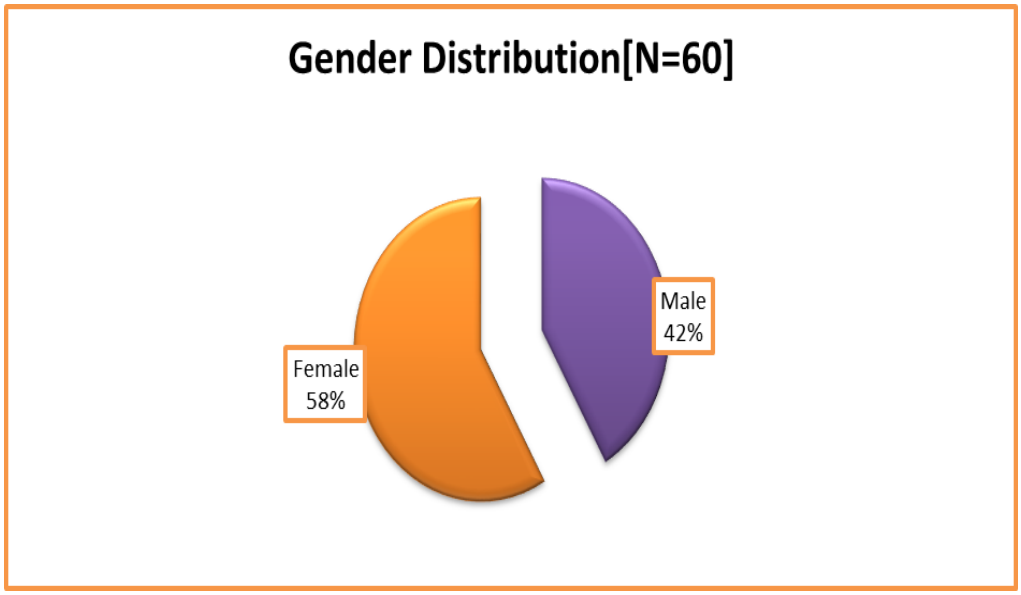
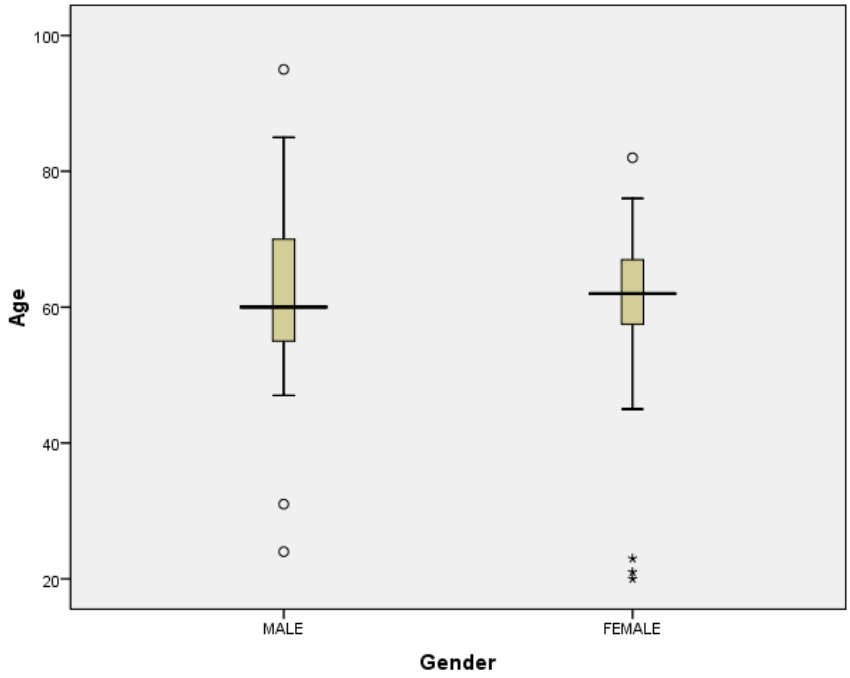


TABLE 4: COMPARISION OF MEAN AGE WITH GENDER

MEAN AGE WITH GENDER							
			95% CI for Mean				
	Mean	**SD**	**Lower**	**Upper**	**Minimum**	**Maximum**	**Sig**
Male	61.76	15.287	55.45	68.07	24	95	
Female	59.69	14.266	54.79	64.59	20	82	>0.05
Total	60.55	14.608	56.78	64.32	20	95	

Among the 60 patients 35 were female and 25 were male patients and male contributed to 42% of the study population and female were 58% (Figure 14). The mean age in male population was 62 years and in female was 60 years. When analyzed on the mean age with gender it was not statistically significant (P>0.05) (Table 4).

FIGURE 15: SCATTER PLOT REPRESENTATION OF MEAN AGE AND GENDER



EMPIRICAL ANTIBIOTIC STARTED

FIGURE16: PERCENTAGE DISTRIBUTION OF EMPIRICAL ANTIBIOTIC STARTED

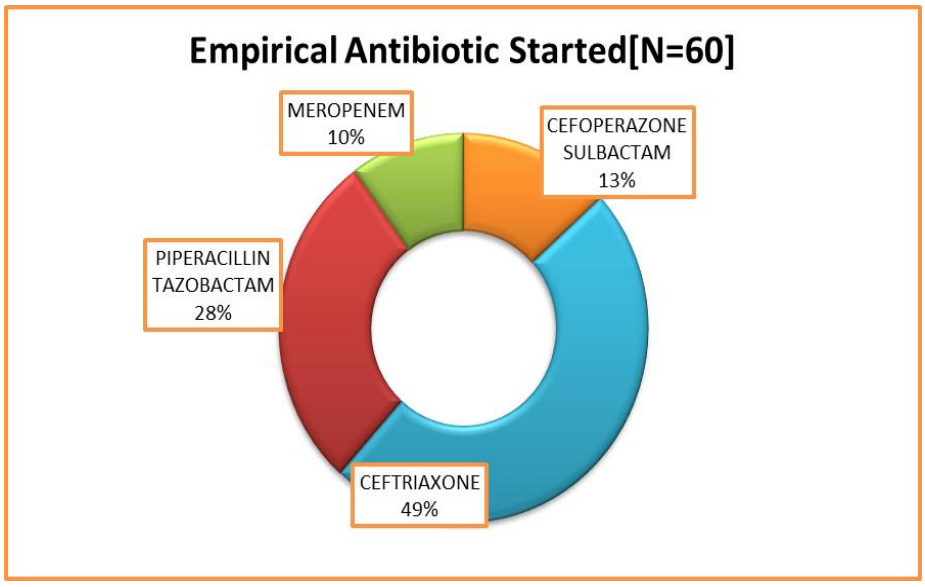


TABLE 5: FREQUENCY OF EMPIRICAL ANTIBIOTIC STARTED

EMPIRICAL ANTIBIOTIC STARTED		
ANTIBIOTIC	**n**	**(%)**
CEFOPREAZONE SULBACTAM	8	**13%**
CEFTRIAXONE	29	**49%**
PIPREACILLIN TAZOBACTAM	17	**28%**
MEROPENEM	6	**10%**
Total	60	**100%**

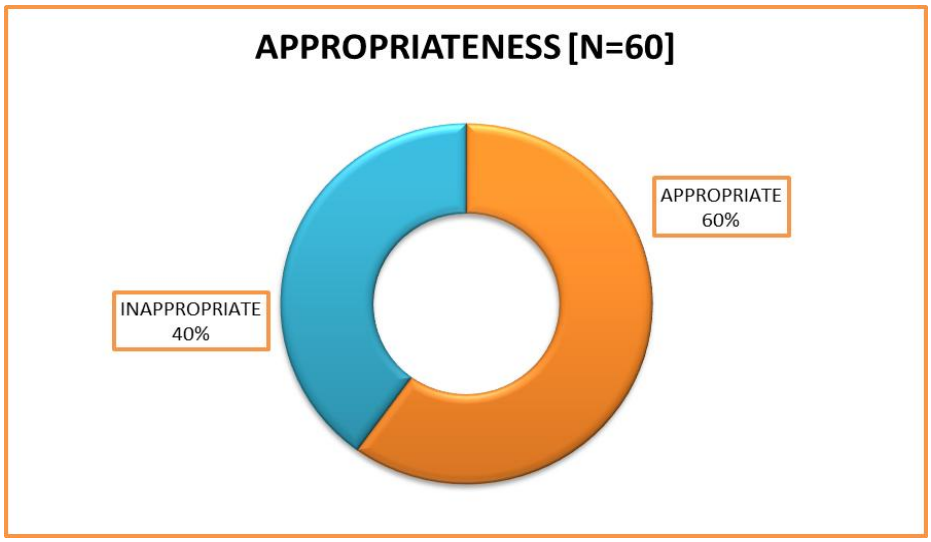
The most common empirical antibiotic started was ceftriaxone which contributed to 49% of the total empirical antibiotics given (figure 16). Next in order was Piperacillin/tazobactam which was started in 28% of the patients. Cefoperazone/sulbactam was administered to 13% of the total patients and followed by Meropenem in 10% (table 5).

APPROPRIATENESS OF ANTIBIOTIC STARTED

TABLE 6: PERCENTAGE DISTRIBUTION OF APPROPRIATENESS OF ANTIBIOTIC STARTED

MODE OF APPROPRIATENESS		
APPROPRIATENESS	n	(%)
APPROPRIATE	36	60%
INAPPROPRIATE	24	40%
Total	60	60%

FIGURE 17: DISTRIBUTION OF APPROPRIATENESS OF ANTIBIOTIC



The empirical antibiotic started was appropriate in a total of 36 (table 6) patients who were around 60% of the total sample and it was inappropriate in 24 patients who were 40% of the study population (figure 17).

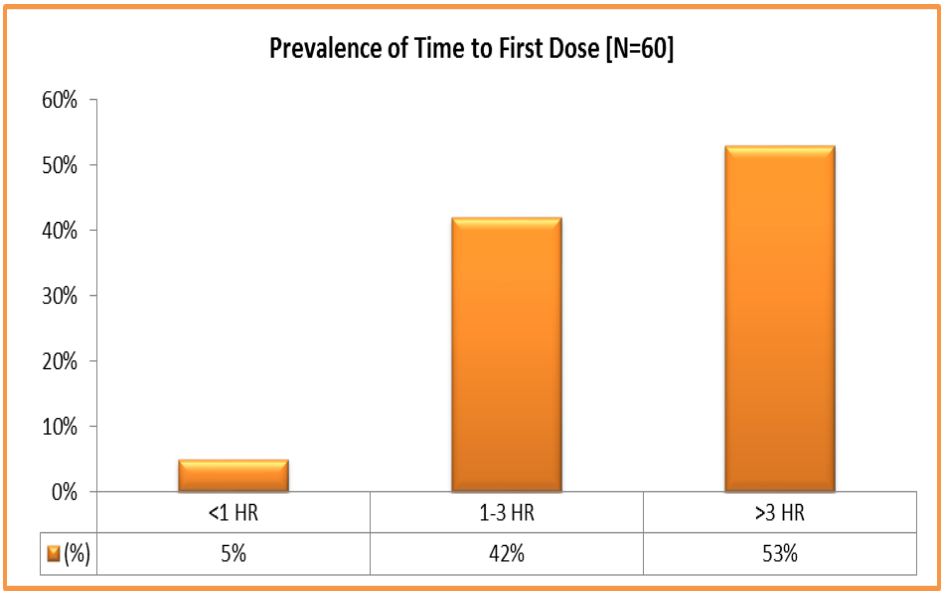
TIME TO FIRST DOSE OF ANTIBIOTIC

Empirical antibiotic was started within 1 hour of suspicion of sepsis in only 3 patients and it was started between 1-3 hours in 25 patients (table 7) which was 42% and the maximum time taken to administer empirical antibiotic was more than 3 hours that was 53% of the total population (figure 18).

TABLE 7

TIME TO FIRST DOSE OF ANTIBIOTIC		
Time	N	(%)
<1 HR	3	5%
1-3 HR	25	42%
>3 HR	32	53%
Total	60	100%

FIGURE 18



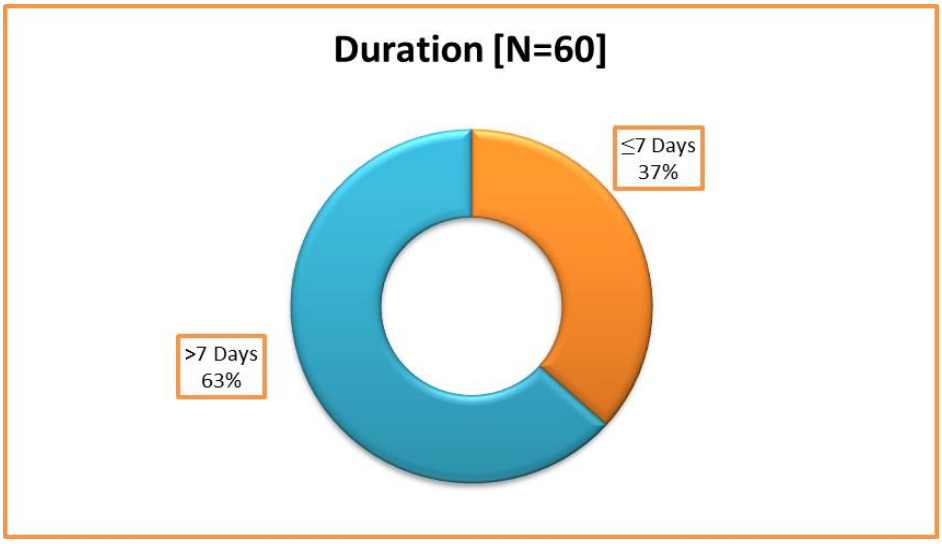
DURATION OF ANTIBIOTIC TREATMENT

Total duration of antibiotic was ≤ 7 days in 37% of the patients but almost 63% of the study patients received antibiotics for more than 7 days (figure 19).

TABLE 8

DURATION OF ANTIBIOTIC TREATMENT		
DAYS	N	(%)
≤7 Days	22	37%
>7 Days	38	63%
Total	60	60%

FIGURE 19



TYPE OF GRAM NEGATIVE ORGANISM GROWN

TABLE 9

TYPE OF ORGANISMS		
ORGANISM	n	**(%)**
E.COLI	13	22%
K.PNEUMONIAE	6	9%
P.AERUGINOSA	3	4%
A.BAUMANI	2	3%
OTHER ORGANISMS	1	2%
K.PNEUMONIAE + P. AERUGINOSA	1	2%
E.COLI + ESBL	22	**37%**
E.COLI+ESBL+AMPC	6	10%
K.PNEUMONIAE + ESBL	2	3%
K.PNEUMONIAE +ESBL+AMPC	1	2%
K.PNEUMONIAE + CARBAPENAMASE	1	2%
A.BAUMANNII + CARBPENAMASE	1	2%
OTHER ORGANISMS + ESBL+AMPC	1	2%
Total	**60**	**100%**

FIGURE 20

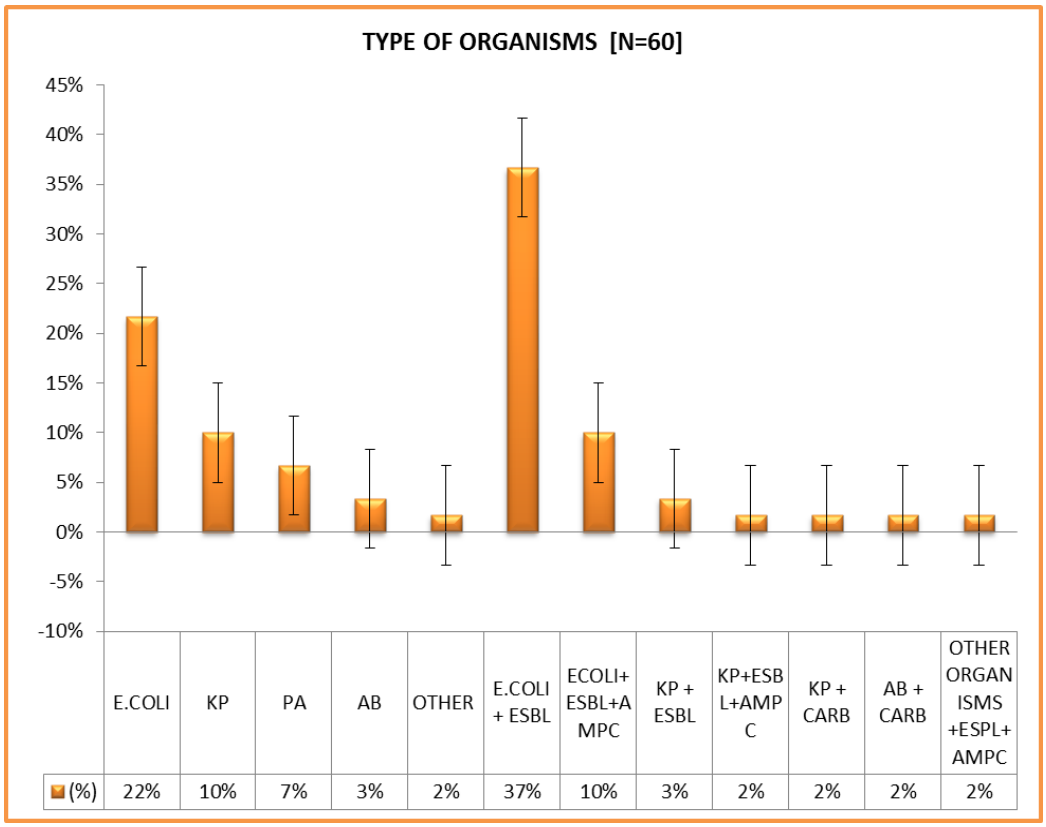


TABLE 10

TOTAL PREVALENCE OF TYPE OF ORGANISMS		
ORGANISM	**n**	**(%)**
E.COLI	41	68%
K.PNEUMONIAE	11	18%
P.AERUGINOSA	4	7%
A.BAUMANNII	3	5%
OTHER ORGANISMS	1	2%

FIGURE 21

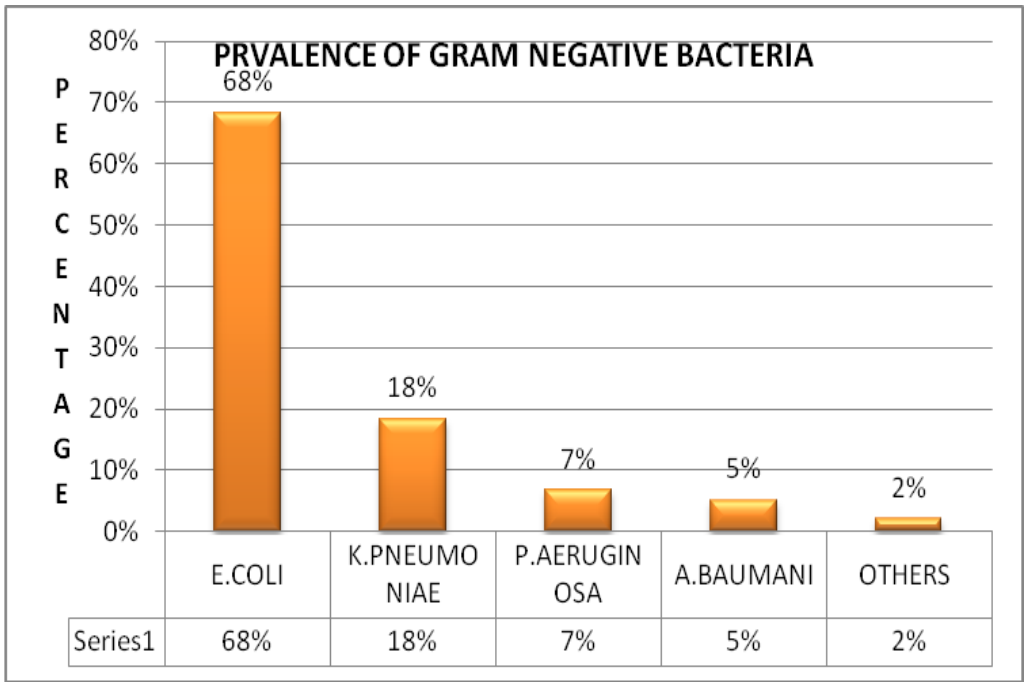
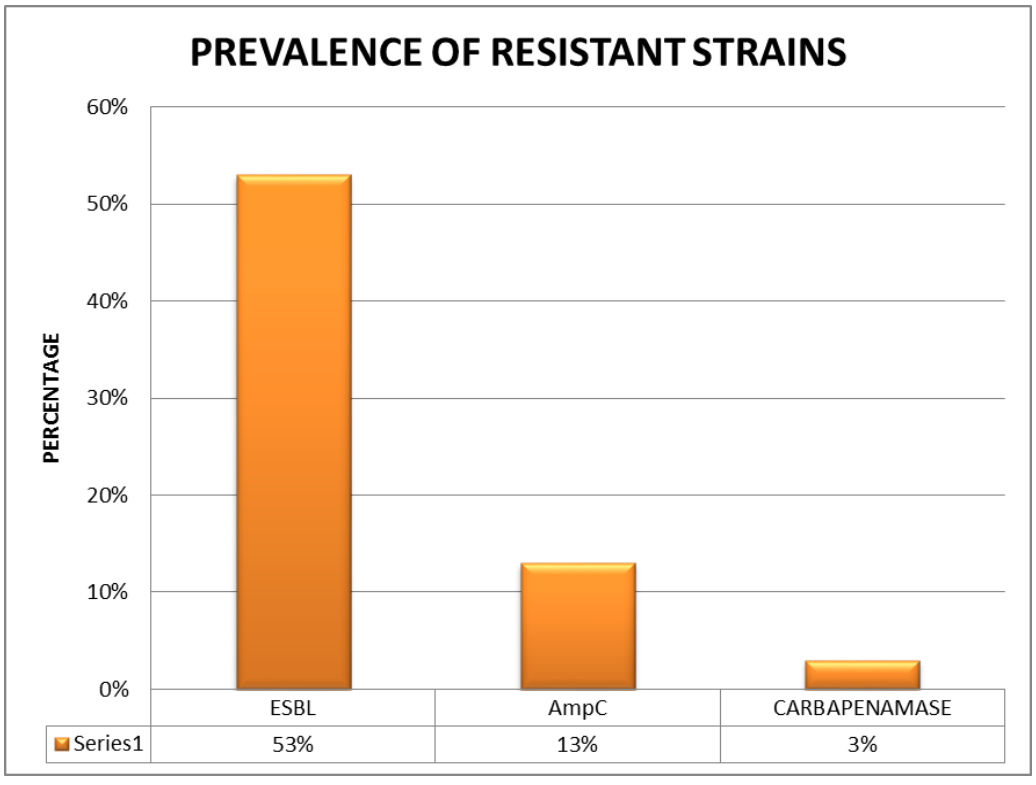


FIGURE 22



Of the 60 study isolates 68% (n = 41) grew E.coli. 18% (n = 11) among the total isolates were K.pneumoniae. 7% grew P.aeruginosa , 5% of the total isolates were A. baumannii and 2% were other organisms (Enterobacter spp.) (figure 21). Among the E.coli grown in 41 isolates ESBL producers were 68% (n=28) , AmpC producers were 14%(n= 6) (table 10). Among the isolates which grew K.pneumoniae , ESBL production was seen in 27% (n=3). Overall prevalence of ESBL was 55% , 13% were AmpC producers and 3% were carbapenamase producers (figure 22). Hence on analysis of the overall pattern of isolates the most common organism was E.coli ESBL , which had a preavalence rate of 37% followed by non ESBL E. coli with prevalence of 22% (figure 20) .

ANTIBIOTIC SUSCEPTIBILITY OF GRAM NEGATIVE BACTERIA

E.coli was highly resistant to third generation cephalosporins with the resistance rate of 76.6% (i.e 23.4% sensitive) followed by fluroquinolones (74%) (figure 23). E.coli was highly sensitive to both Aminoglycosides and Carbapenems whose sensitivity was 98.8%. E.coli also had a noteworthy sensitivity to Betalactam/ betalactamse inhibitors of about 85.8% (figure 23).

K.pneumoniae exhibited notable sensitivity to carbapenems (92%) , followed by Betalactam/ betalactamase inhibitor (88%) and Aminoglycosides (85%). K.pneumoniae exhibited equal resistance to both Fluroquinolones and Third generation cephalosporins in 55% of the isolates (figure 24).

FIGURE 23

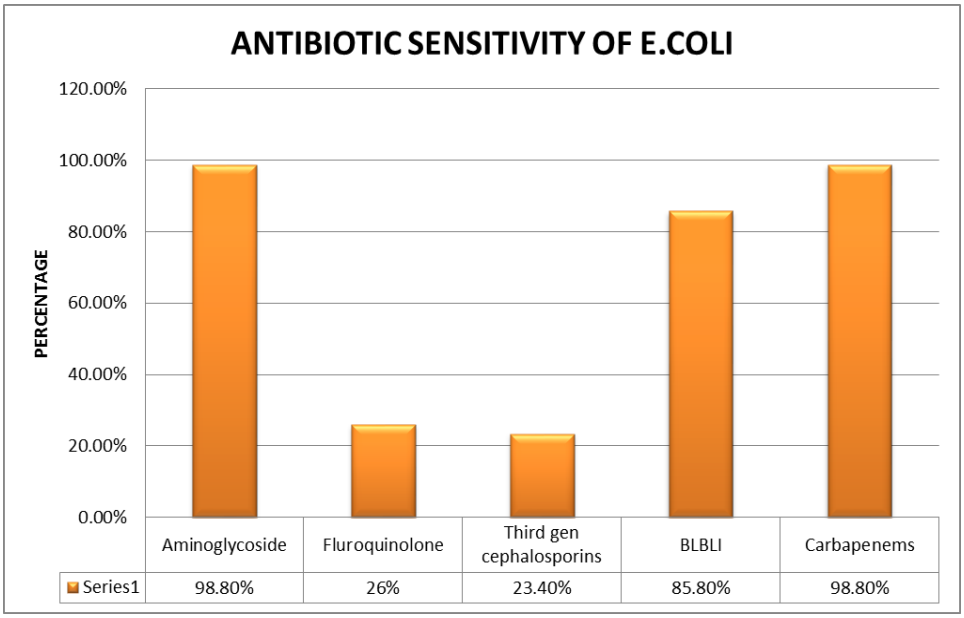
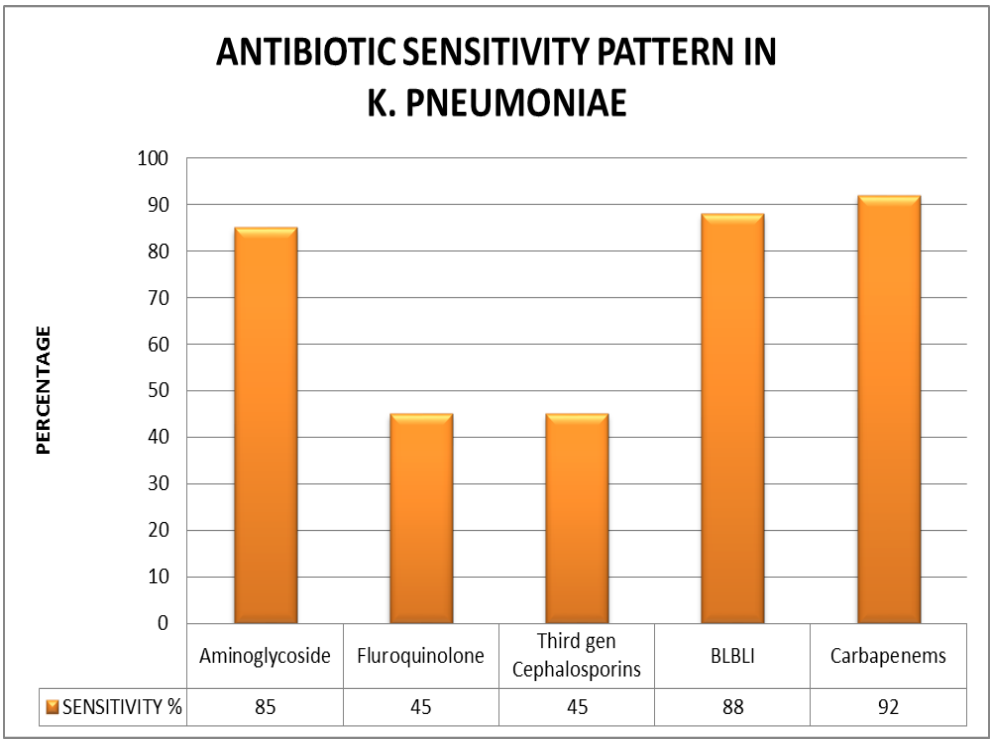


FIGURE 24



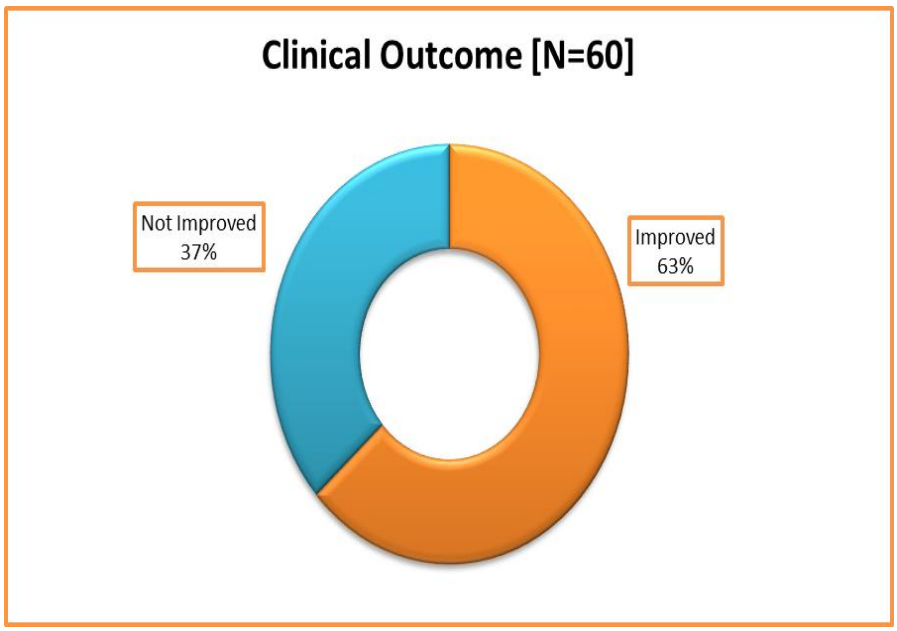
CLINICAL OUTCOME

Of the total 60 patients clinical improvement in terms of decreasing serial MSOFA scoring was found in 38 patients (table 11) which was 63% of the total study population. 22 patients did not improve and it contributed to 37% of the total sample studied (figure 25).

TABLE 11

Outcome	n	(%)
Improved	38	63%
Not Improved	22	37%
Total	60	100%

FIGURE 25



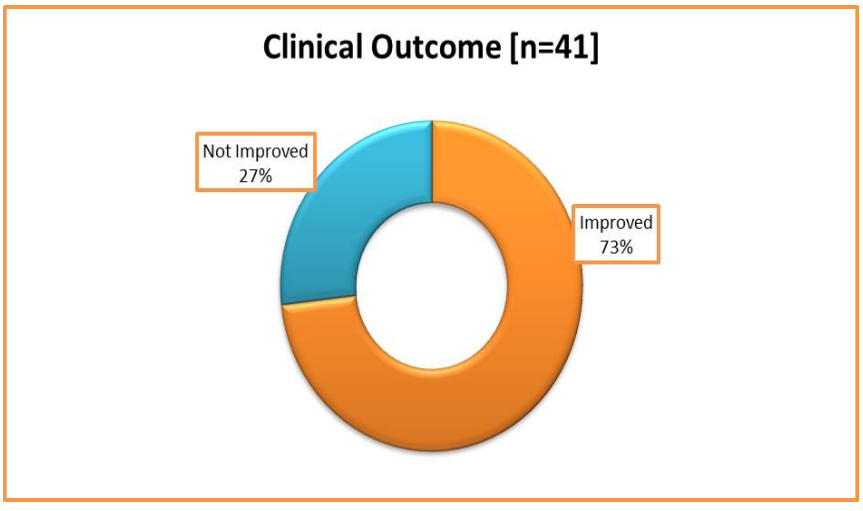
CLINICAL OUTCOME OF VARIOUS GRAM NEGATIVE ORGANISMS

Of the 41 isolates which grew E.coli 73% showed good clinical outcome (figure 26), of 11 isolates which grew K.pneumoniae 55% of the patients showed a good clinical outcome and 45% did not improve (figure27). None of the patients with Pseudomonas spp and Acinetobacter baumannii infection improved (figure 28, 29).

TABLE 12

Clinical outcome of E.COLI	
Out come	n
Improved	30
Not Improved	11
Total	41

FIGURE 26

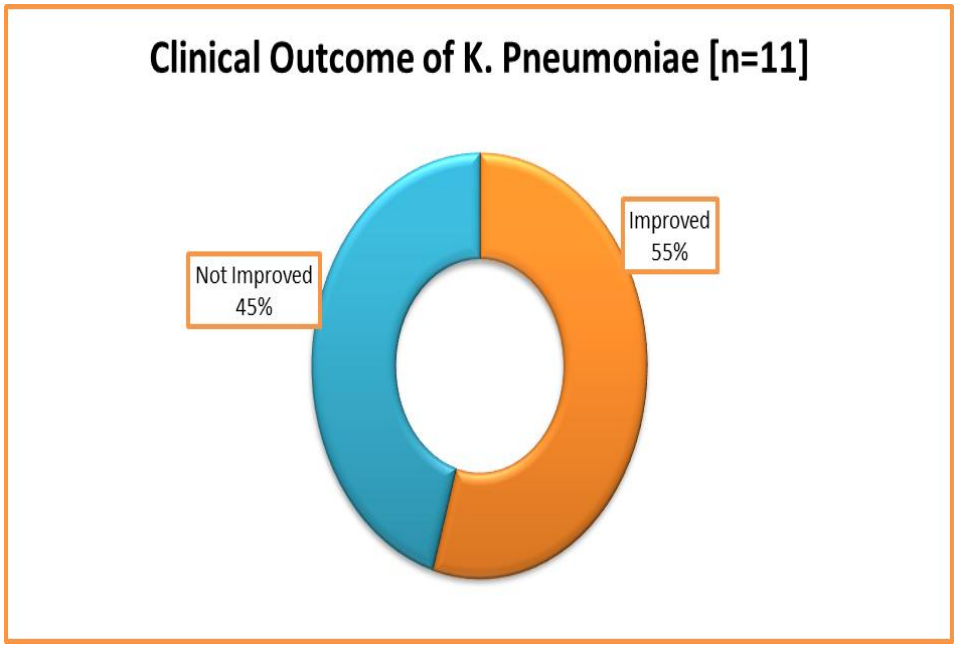


CLINICAL OUTCOME OF K. PNEUMONIAE

TABLE 13

Clinical outcome of K .Pneumoniae	
Outcome	n
Improved	6
Not Improved	5
Total	11

FIGURE 27



CLINICAL OUTCOME OF P.AERUGINOSA

TABLE 14

Out come	n
Improved	0
Not Improved	4
Total	4

FIGURE 28

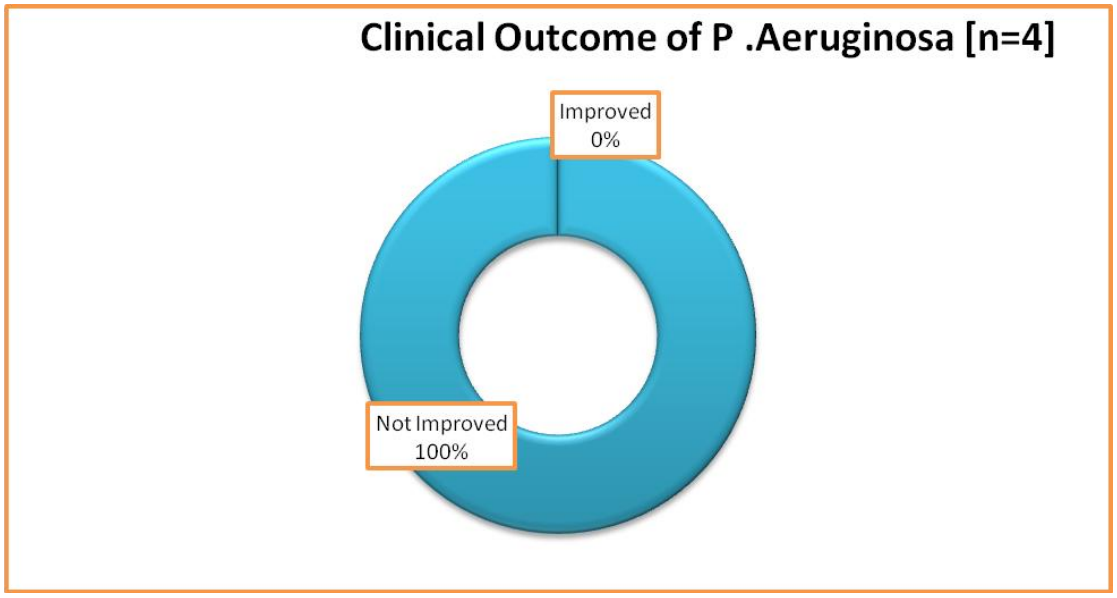
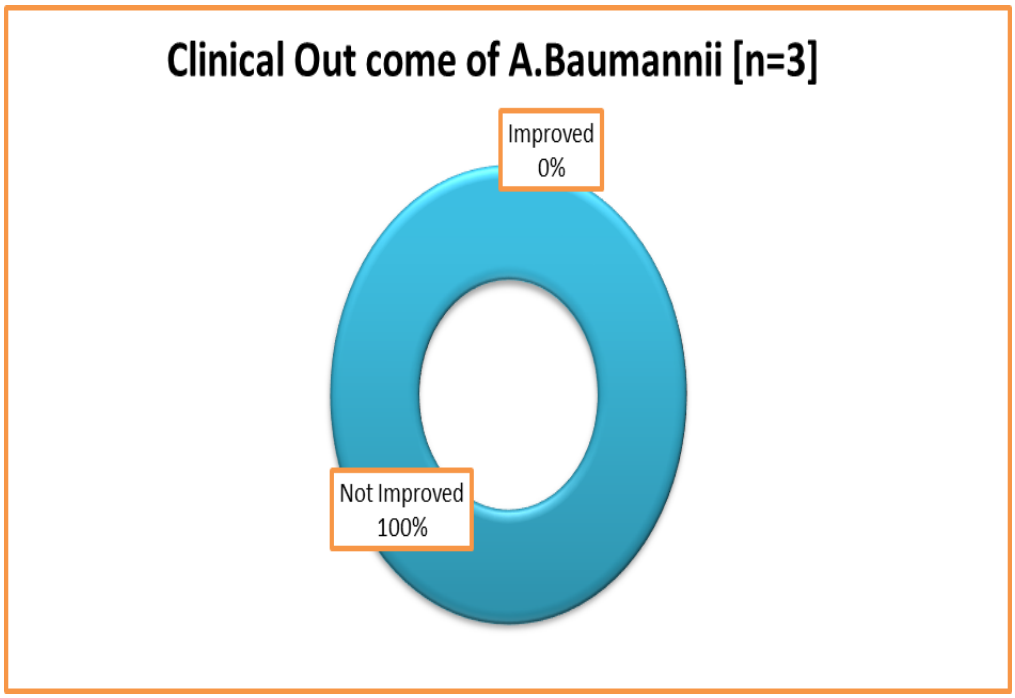


TABLE 15

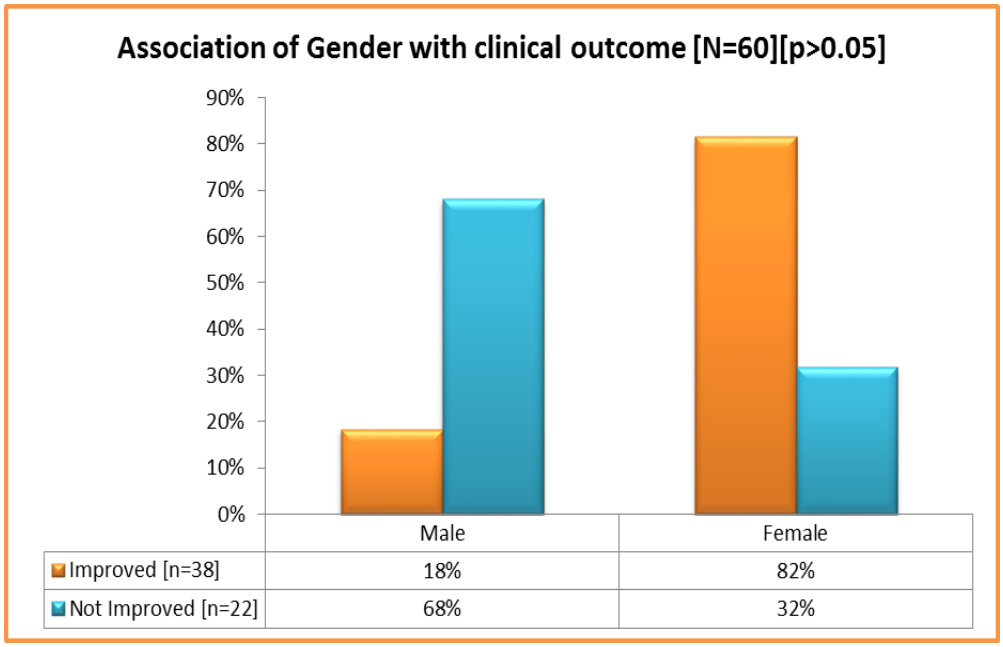
Clinical outcome of Acinetobacter Baumannii	
Out come	n
Improved	0
Not Improved	3
Total	3

FIGURE 29



ASSOCIATION OF AGE AND GENDER WITH CLINICAL OUTCOME

FIGURE 30



Of the total of 22 patients who did not improve male were 68% and female were 32% and of the 38 patients who improved 82% were female and 18% were male patients (table 16).

The p value was > 0.05 suggesting that there was no association between gender and clinical outcome in the study population.

TABLE 16

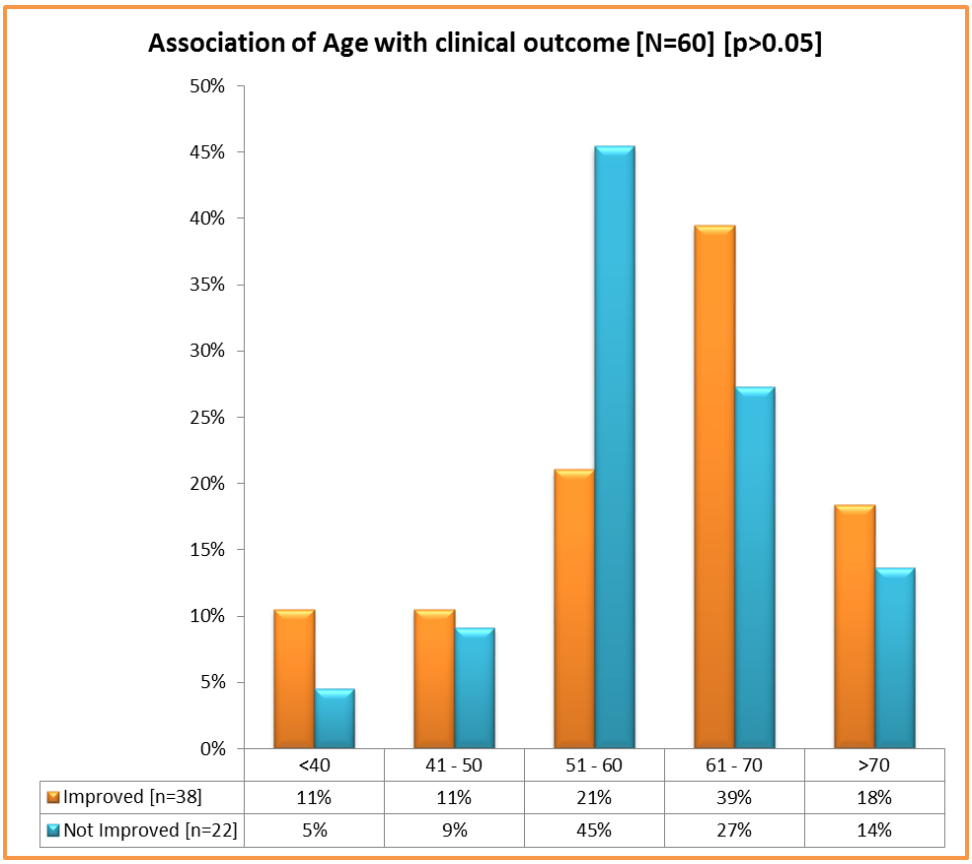
Association of Gender with Clinical Outcome			
	Outcome		
Gender	Improved	Not Improved	Total
Male	7	15	22
Female	31	7	38
Total	38	22	60

ASSOCIATION BETWEEN AGE AND CLINICAL OUTCOME

TABLE 17

Association of Age with Clinical Outcome			
	Outcome		
Age	Improved	Not Improved	Total
<40	4	1	5
41 - 50	4	2	6
51 - 60	8	10	18
61 - 70	15	6	21
>70	7	3	10
Total	38	22	60

FIGURE 31



Of the 38 patients who improved the age group were maximum clinical improvement was seen was between 61-70 years of age which was 39% of the total patients who improved (table 17). Of the 22 patients who did not improve the range of age group was between 51-60 which was 45% of the total patients who did not improve (figure 31).

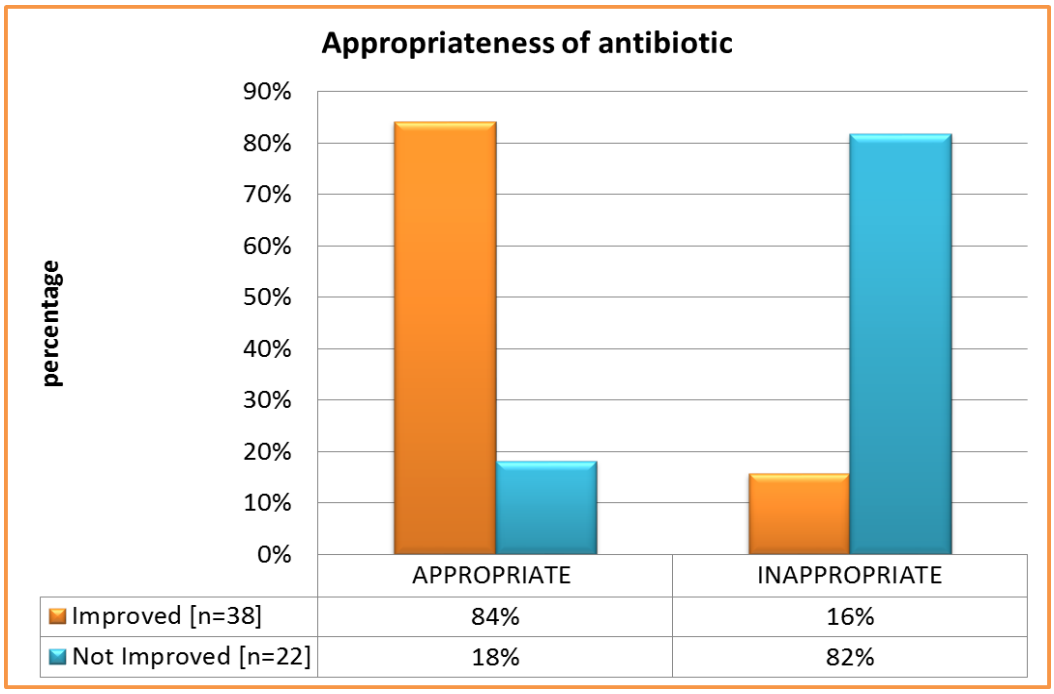
ASSOCIATION BETWEEN APPROPRIATENESS OF ANTIBIOTIC AND CLINICAL OUTCOME

TABLE 18

Association of Mode of Appropriateness with Clinical Out come			
	Outcome		
APPROPRIATENESS	Improved	Not Improved	Total
APPROPRIATE	32	4	36
INAPPROPRIATE	6	18	24
Total	38	22	60

Among the 60 patients 36 patients received an appropriate empirical antibiotic therapy and 24 patients did not receive an empirical antibiotic (table 18). Of the 36 patients who received empirical antibiotic therapy appropriately 32 showed good clinical outcome and it contributed to 84% and in the group of 24 patients who had received an inappropriate empirical antibiotic therapy 18 patients showed poor clinical outcome and it was 82%. In the remaining patients in the appropriate antibiotic group only 4 did not have a good clinical outcome which was 18% (figure 32).

FIGURE 32



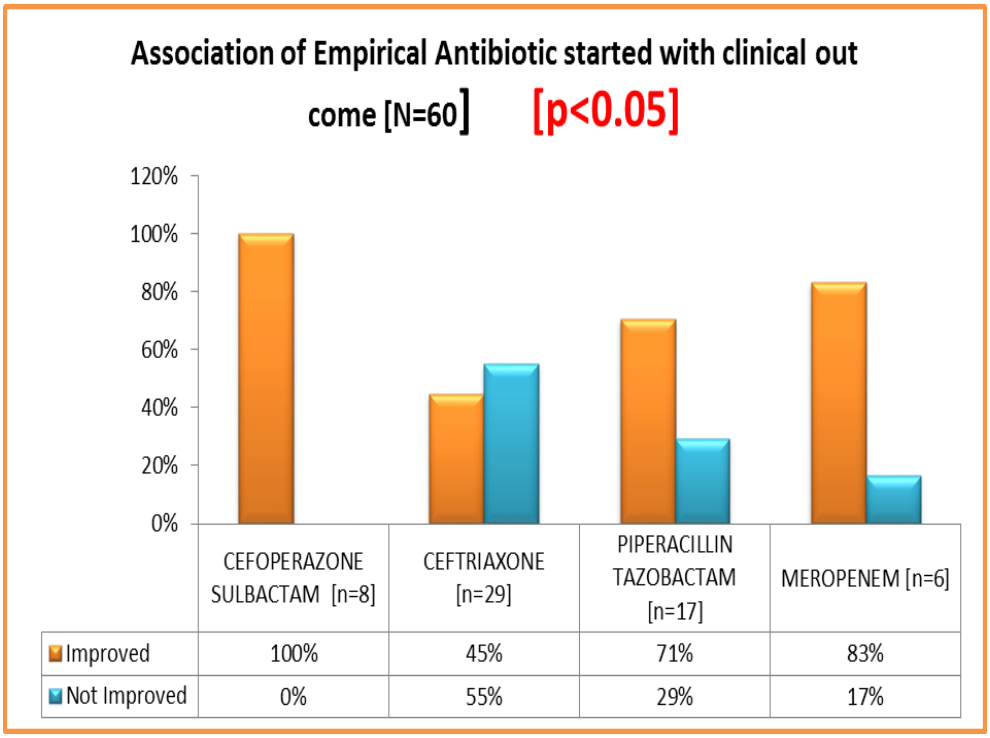
ASSOCIATION OF EMPIRICAL ANTIBIOTIC STARTED WITH CLINICAL OUTCOME

TABLE 19

ANTIBIOTIC	Out come		Total
	Improved	Not Improved	
CEFOPREAZONE SULBACTAM	8	0	8
CEFTRIAXONE	13	16	29
PIPREACILLIN TAZOBACTEM	12	5	17
MEROPENEM	5	1	6
Total	38	22	60

Of the 8 patients who received cefoperazone/ sulbactam 100% clinical improvement was seen and in those who received ceftriaxone as an empirical antibiotic of choice 45% showed clinical improvement and 55% did not improve (table 19). Of the 17 patients who received piperacillin/tazobactcam 71% showed good clinical outcome wheras 29% did not improve. Of the 6 patinets who recived meropenem 83% showed good clinical outcome wheras 17% did not improve clinically. The maximum clinical outcome was seen with cefoperazone/sulbactam and least with ceftriaxone. The p value was <0.05 suggesting that there is a association between empirical antibiotic started and clinical outcome (figure 33).

FIGURE 33



ASSOCIATION OF TIME TO FIRST DOSE OF ANTIBIOTIC AND CLINICAL OUTCOME

Of the patients who improved the shortest time taken to administer empirical antibiotic was 1 hour. Among the patients who did not improve the longest tome taken to administer antibiotic was 7 hours. The mean time for antibiotic administration for the group of patients who improved was 2 hours and the mean time for antibiotic administration for the patients who did not improve was 4 hours (table 20).

TABLE 20

Mean Time to first dose in hours with clinical out come							
			95% CI for Mean				
Out come	**Mean**	**SD**	**Lower**	**Upper**	**Minimum**	**Maximum**	**Sig**
Improved	2.89	0.981	2.57	3.22	1	5	
Not Improved	4.05	1.174	3.52	4.57	2	7	**<0.001**
Total	3.32	1.186	3.01	3.62	1	7	

All patients who received antibiotic within 1 hour of suspicion of sepsis showed good clinical outcome. Of the 38 patients who improved 76% of the patients received antibiotic within 3 hours and 91% of the patients did not improve when antibiotic was administered after 3 hours. The association was significant ($p<0.05$) suggesting a significant association between timing of antibiotic and clinical outcome (figure 34).

FIGURE 34

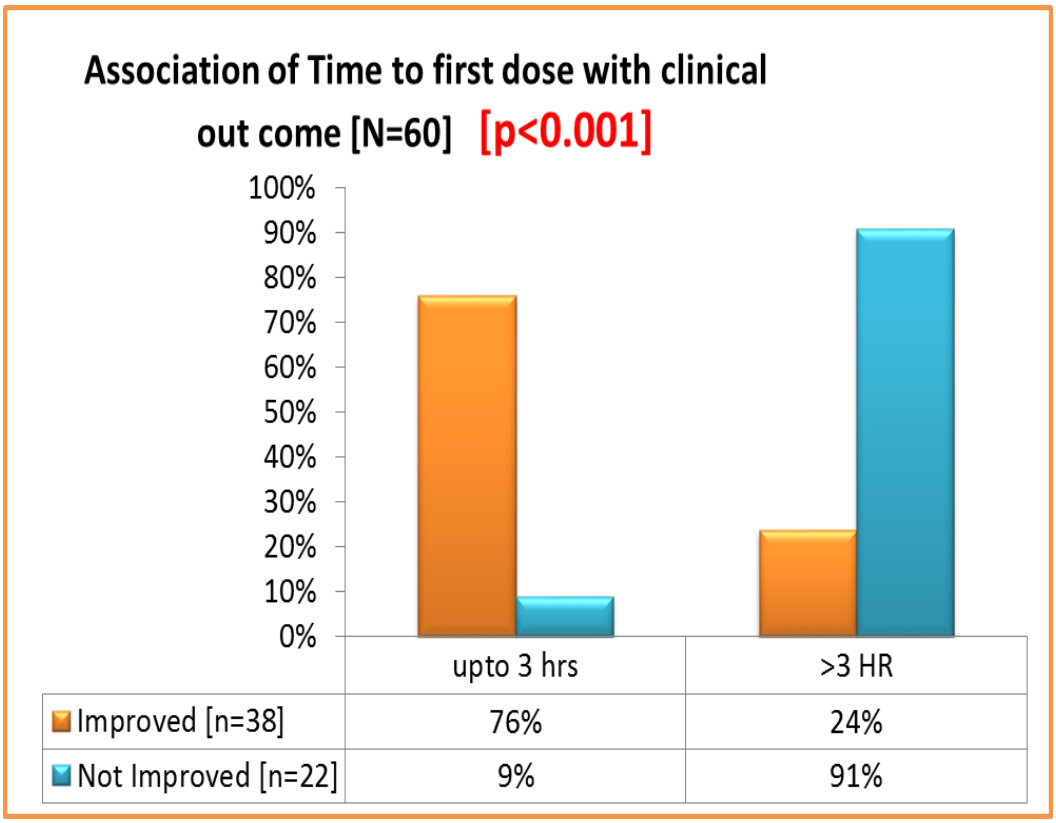
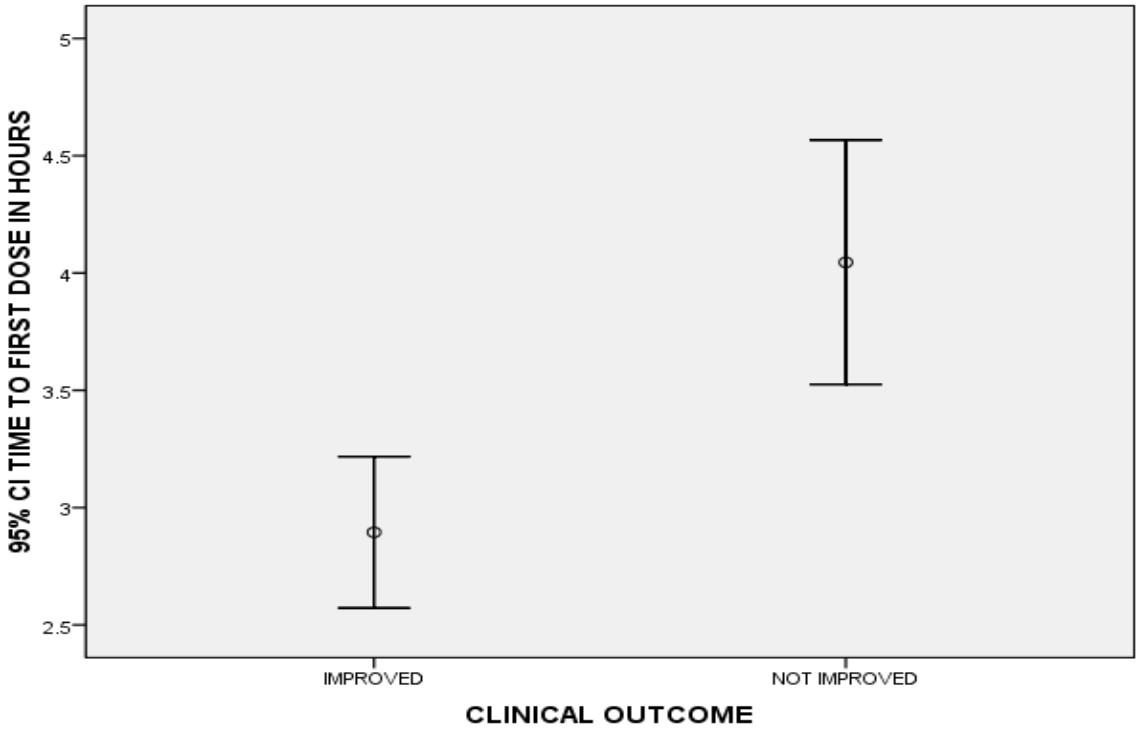


FIGURE 35



ASSOCIATION BETWEEN DURATION OF ANTIBIOTIC AND CLINICAL OUTCOME

TABLE 21

Association of Duration of antibiotic with Clinical Outcome			
	Out come		
DAYS	Improved	Not Improved	Total
<7 Days	7	15	22
> 7 Days	31	7	38
Total	38	22	60

FIGURE 36

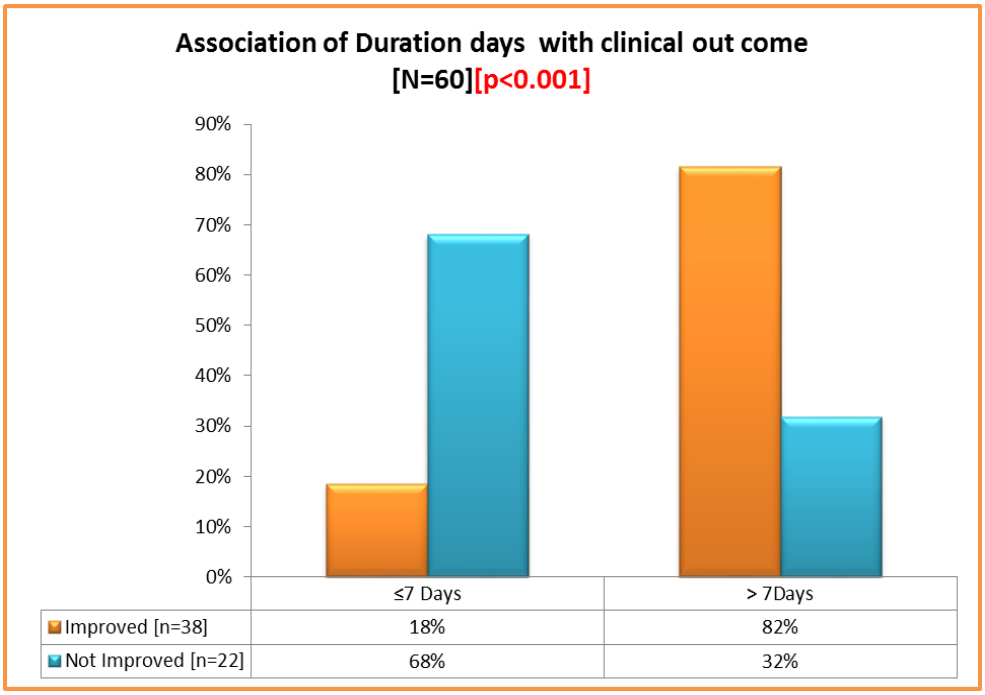
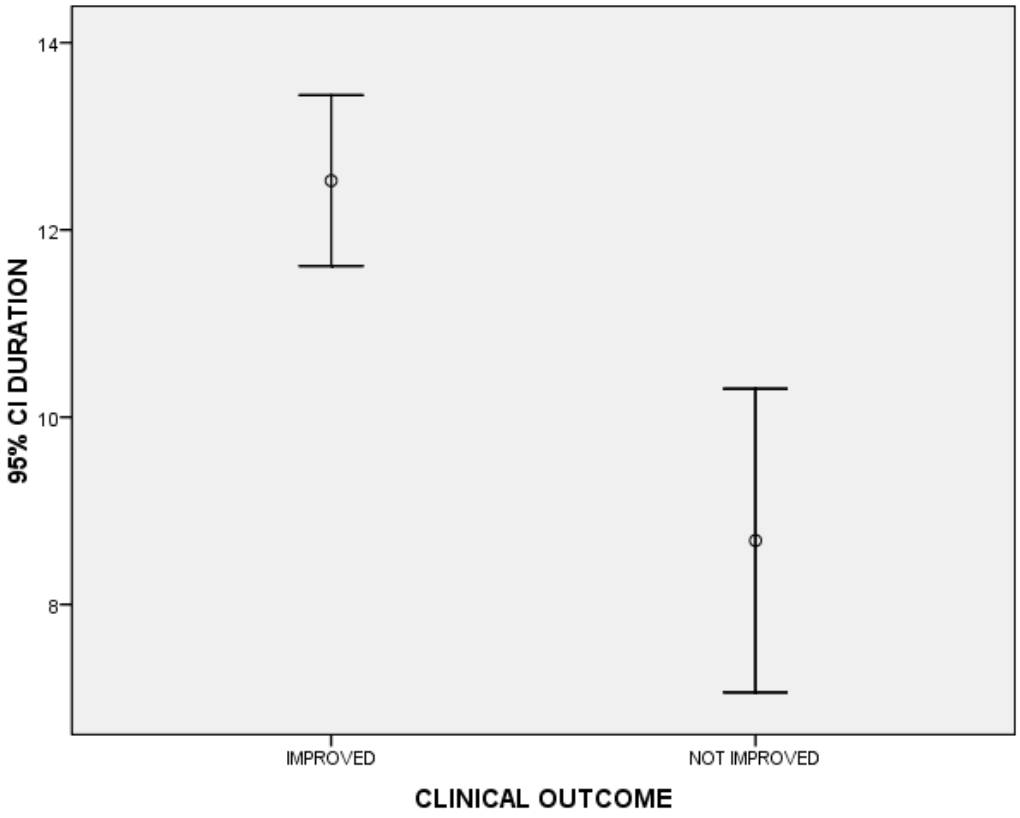


TABLE 22

Mean Duration of antibiotic therapy with clinical outcome

Out come	Mean	SD	95% CI for Mean		Minimum	Maximum	Sig
			Lower	Upper			
Improved	12.53	2.778	11.61	13.44	7	14	
Not Improved	8.68	3.657	7.06	10.3	2	14	<0.001
Total	11.12	3.618	10.18	12.05	2	14	

FIGURE 37



Among the 60 patients, 22 patients received definitive antibiotic therapy for less than 7 days and out of the 22 patients 15 did not improve (table 21). They were about 68% of the total patients who did not have a good clinical outcome. Of the 38 patients who received a definitive antibiotic therapy for more than 7 days 82% of the patients showed good clinical improvement (figure 36). The mean duration of antibiotic administration was 13 days in patients who improved and 9 days for patients who did not have a good clinical outcome(table 22). The p value was <0.001 which shows a significant association between duration of antibiotic treatment and clinical outcome (figure 37).

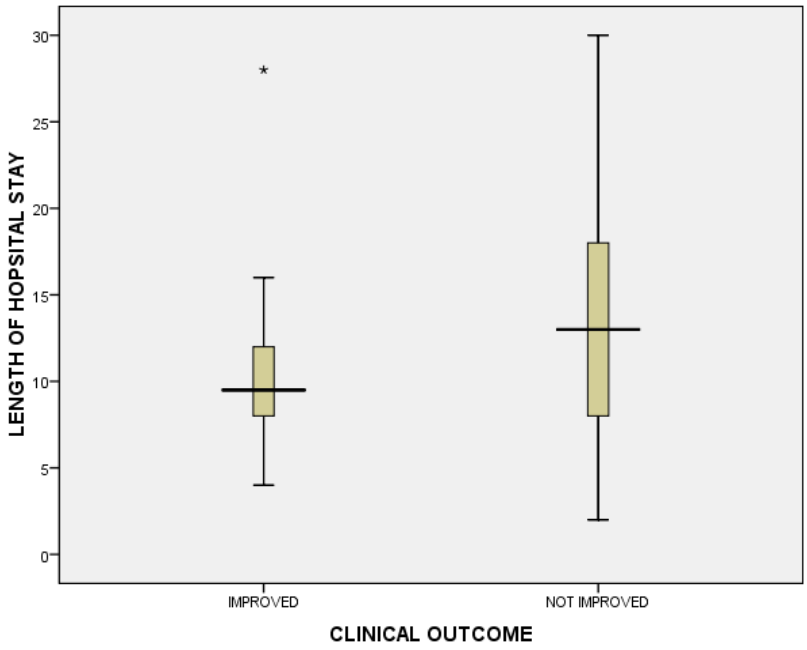
ASSOCIATION BETWEEN MEAN LENGTH OF HOSPITAL STAY AND CLINICAL OUTCOME

The mean duration of hospital stay in the patients who improved was 14 days(table 23) and there was a significant statistical association between mean length of stay and clinical outcome(figure 38).

TABLE 23

Mean Length of hospital days with clinical outcome							
			95% CI for Mean				
Out come	Mean	SD	Lower	Upper	Minimum	Maximum	Sig
Improved	10.32	4.375	8.88	11.75	4	28	
Not Improved	14.18	7.613	10.81	17.56	2	30	<0.05
Total	11.73	6.014	10.18	13.29	2	30	

FIGURE 38



ASSOCIATION BETWEEN MSOFA SCORING AND CLINICAL OUTCOME

The Modified sequential organ function assessment scoring was calculated initially and repeated after 72 hours and the following results were obtained. The mean initial MSOFA score in the patients who improved was 4 and the mean initial MSOFA score for the patients who did not improve was 8. The statistical difference between the two means was significant ($p<0.05$) and this is confirmed by error plot method (table 24).

The MSOFA score repeated showed a mean value of 1 in patient who improved and 11 in patient who did not improve. The statistical difference between the two means were significant with p value < 0.05 (table 25). The error plot marked with 95% confidence interval showed a significant association of difference between the two means.

TABLE 24

Mean INITIAL MSOFA score with clinical outcome							
			95% CI for Mean				
Out come	Mean	SD	Lower	Upper	Minimum	Maximum	Sig
Improved	4	2.20	3.01	4.46	0	10	
Not Improved	8	4.41	6.32	10.23	2	14	**<0.001**
Total	5	3.85	4.41	6.39	0	14	

FIGURE 39

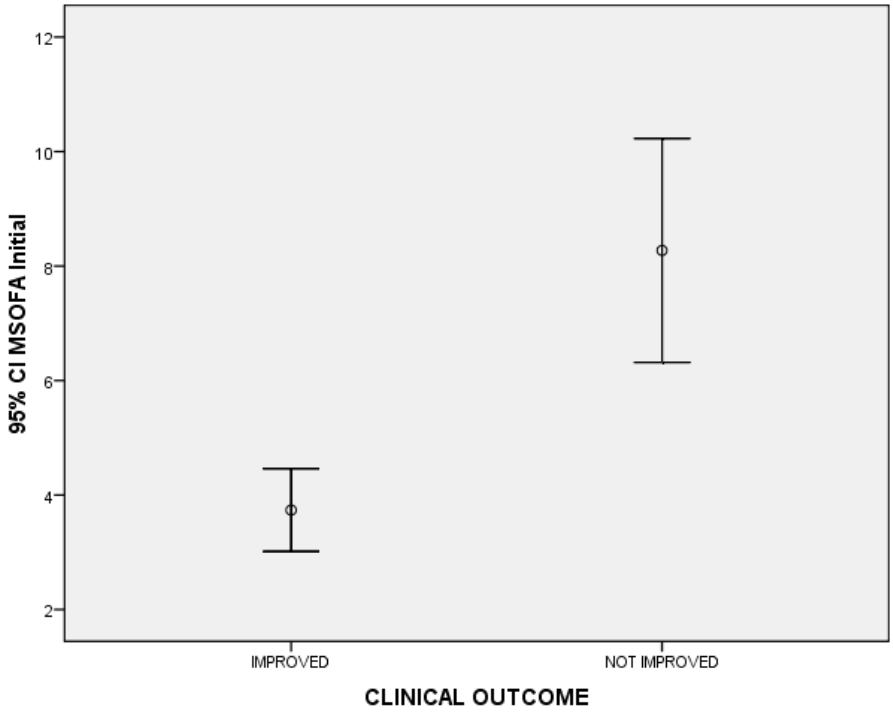
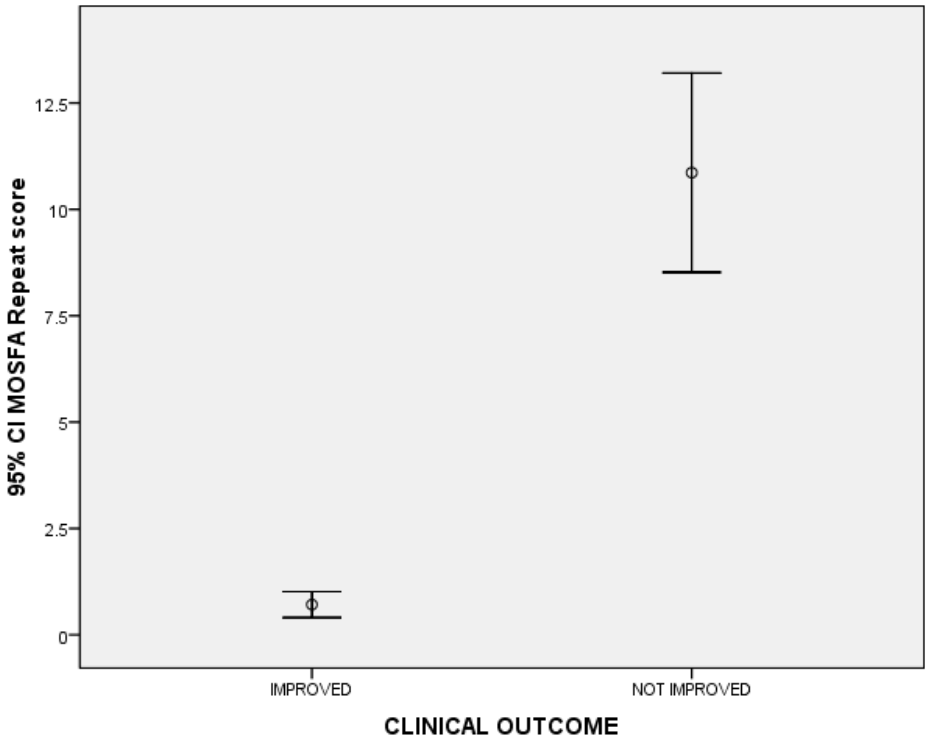


TABLE 25

Mean REPEAT MSOFA score with clinical out come							
			95% CI for Mean				
Out come	Mean	SD	Lower	Upper	Minimum	Maximum	Sig
Improved	1	0.9	0.41	1.02	0	4	
Not Improved	11	5.3	8.52	13.21	2	21	**<0.001**
Total	4	5.9	2.91	5.96	0	21	

FIGURE 40


95% CI MOSFA Repeat score
12.5
10
7.5
5
2.5
0
IMPROVED
NOT IMPROVED
CLINICAL OUTCOME

DISCUSSION

Our study was a prospective study on 60 patients identified with gram negative bacteria in blood culture isolates. The study evaluated the prevalence , antibiotic susceptibility and the clinical outcome of gram negative bacteremia. We also analyzed on different possible parameters that would influence the clinical outcome of gram negative bacteremia.

Our study population was mostly between the age group of 61-70 years of age and predominantly females (n=35, 58%). Most of the studies on gram negative bacteremia have reported the mean age group between 50-80 years of age. When evaluated, age and gender did not have a significant statistical association with clinical outcome ($p>0.05$).

The most common empirical antibiotic started was ceftriaxone in almost half of the study population (n=29 , 49%) followed in order by piperacillin / tazobactam (n=19, 28%), others where started on either cefoperazone sulbactam or meropenem. The antibiotic of choice was mostly based on presence or absence of septic shock, previous antibiotic exposure, comorbid illness.

Initial antibiotic of choice was appropriate (i.e presence of in vitro susceptibility to the antibiotic chosen) in 60% (n=36) of the patients and inappropriate in 40% (n=24). The importance of timing of antibiotic was evaluated in many studies and most of the studies have concluded that earlier

the administration of antibiotic, better is the clinical outcome in many aspects like duration of hospital stay, decrease in mortality and morbidity. Surviving sepsis campaign insists on the initiation of empirical antibiotic within 1 hour of suspicion of sepsis. In our study only 5% (n=3) of the patients received first dose of empirical antibiotic therapy. Almost half of the patients received antibiotic >3 hours after suspicion of sepsis (n=32 , 53%) which is considerably greater. The possible delay in administration of antibiotic could be delay in diagnosis, cost factors, drug hypersensitivity or increase in transportation time.

In our study there was a high prevalence of E.coli (n=41, 68%) bacteremia followed in order by K.pneumoniae (n=11 , 18%) P.aureginosa , Acinetobacter baumannii and Enterobacter spp. were reported in 7% , 5% and 2% respectively. This study has noted a high prevalence of E.coli compared to other studies done in South India where they had reported prevalence rate of 30-60% for E.coli. The possible explanation for such prevalence rates could be, our study included only patients identified with gram negative bacteremia whereas other reported studies included both gram positives and gram negatives and most of the study population were from ICU and those studies were reported few years ago. Other studies have reported the prevalence of other gram negative organisms like P. aeruginosa and A. baumannii in frequency range between 19-24%, 8-10%, 5-8% respectively. Our study has also reported nearly in the same range as the other studies.

When analyzed on the prevalence of resistant strains among gram negative bacteria our study has found that of the total of 60 gram negative isolates 53% were ESBL producers, 13% were AmpC producers and 3% were carbapenamse producers and remaining were normal strains. When viewed separately for individual species more than half of the total E.coli isolates (28 of 41) were ESBL producers. E.coli ESBL was the highest reported growth (37%) in our study compared to normal strains of E.coli whose prevalence was 22%. 77% of the E.coli isolates were resistant to third generation cephalosporins and 74% resistant to Fluroquinolones. E.coli was least resistant to carbapenem (2.2%) followed by BLBLI (15%). This pattern of antibiotic resistance was similar to many of the studies reported by Balan et al, Waghmare et al, Rajeevan et al. These studies have also reported the resistance rates of E.coli to cephalosporins between 50-65% which is comparatively lower compared to our study whereas resistance to other group of antibiotics were nearly in the same order. The reason for increased resistance to fluroquinolones and cephalosoprins among E.coli in our study could be due to high prevalence of ESBL producing strains which was comparatively lower in other studies.

Among K.pneumoniae maximum resistance was reported to Cephalosporins and fluroquinolones which showed 55% resistance. K. pneumonia was resistant to carbapenems in 8% and 12 % to BLBLI and 18% to aminoglycosides. Most of the studies have reported resistance of K.pneumoniae to fluroquinolones between 40-60% and cephalosporins

between 50-75% and carbapenems between 0-5% which is consistant with our data.

Clinical outcome was analyzed in terms of either improving or worsening MSOFA scores. Parameters like timing of administration of antibiotic, appropriateness of empirical antibiotic started, duration of antibiotic and their association with clinical outcome was analyzed in our study.

On analysis it was found that 38 of the 60 patients (63%) had a good clinical outcome whereas 37% did not improve as evidenced by worsening MSOFA scores. When analyzed on the outcome of individual bacterial species, 73% of the patients with E. coli bacteremia and 55% of the patients with K.pneumoniae improved. None of the patients with P.aeruginosa and A. baumannii improved. The potential reason for poor outcome in these two groups would be both these being a hospital acquired infection, initial MSOFA for these patients were high and were admitted in ICU. Most of them received an inappropriate empirical antibiotic as evidenced by our study where most of the patients were started on a third generation cephalosporin preferably ceftriaxone. Also other factors like associated risk factors, source of infection, duration of ICU stay, dose and duration of antibiotcs also influences on outcome.

Further analysis on appropriateness of empirical antibiotic and its association with clinical outcome showed a significant statistical association between the two (<0.05). It was found that outcome was good when

appropriate antibiotic was given. 84% of the patients in the appropriate antibiotic group had a good outcome. In the same way 82% of the patients in the inappropriate antibiotic group did not improve.

MONARCS trial and studies by Leibovici et al, Behrendt et al has also reported that there has been a significant reduction in mortality of about 10-15% when an appropriate antibiotic was chosen. Likely reason for initiation of inappropriate antibiotic would be the pattern of antibiotic sensitivity pattern of various gram negative isolates which have changed over the past few years because of increasing prevalence of resistant strains and also other economic issues of the patient which would have prevented in opting for a higher antibiotic.

Timing of administration of empirical antibiotic also plays a vital role in clinical outcome of any sepsis as its importance has been stressed in many of the sepsis guidelines and the recent Third International Consensus definition for sepsis and septic shock has quoted the same in its guidelines that appropriate antibiotic should be administered within 1 hour of suspicion of sepsis. Our study has found that the mean time to antibiotic administration in patients who improved was 2 hours whereas it was 7 hours in patients who did not improve.

The rate of clinical improvement in the patient who received appropriate antibiotic was 76% whereas 91% of the patients did not improve in the inappropriate treatment group. Our study also found a significant statistical

association between duration of antibiotic and clinical outcome ($p<0.001$). The mean duration of antibiotic administration was 13 days in the clinically improved group whereas it was 9 days in those who did not improve. The percentage of good clinical outcome was comparatively higher in the longer duration of antibiotic group when compared to less than 7 days. The outcome was 82% in the patients who received antibiotics for more than 7 days.

Our study also found a significant association between the empirical antibiotic of choice and clinical outcome. Poor outcome rate was noted in the patients who received ceftriaxone (55%). Substantially good outcome was reported in cefoperazone/ sulbactam (100%) , piperacillin / tazobactam (71%) and meropenem (83%).

Considering the above pattern of outcome and also the increased prevalence of drug resistance strains it is obvious that the pattern of empirical antibiotic prescription has to be revised such that a switchover has to be made from choosing a cephalosporin to a broad spectrum antibiotic most preferably a BLBLI.

Our study has also noted a significant association between MSOFA scoring, length of hospital stay and clinical outcome. Though our study has found a significant association between timing of antibiotic, choice of empirical antibiotic, duration of antibiotic, MSOFA scoring on the clinical outcome there are some limitations in the study which has to be addressed.

Our study was only a prospective study involving only a small sample size of 60 patients with gram negative bacteremia, hence propagating this result to the entire population is not promising. The study on antibiotic susceptibility was only based on in vitro susceptibility reported by the laboratory but other factors other than the above mentioned factor like dose of the antibiotic given, drug activity etc were not analyzed in detail.

We enrolled all patients with gram negative septicemia irrespective of the severity of sepsis comprising both ICU and non ICU patients so the results could have been varied. Many unmeasured variables like quality of care could not be assessed which would have influenced the outcome. Other factors which would have influenced the outcome like comorbid illness , organ dysfunction , source of infection would also have confounded the results of our study.

CONCLUSION

To conclude our study on gram negative bacteremia has shown high prevalence of E. coli, another remarkable finding in our analysis was high prevalence to ESBL strains compared to non ESBL strains. We have also found a significant relationship between the appropriate empirical antibiotic of choice and clinical outcome. The change in antibiotic sensitivity pattern among the gram negative bacteria was noted in our study where significant resistance was noted in cephalosporin group. Keeping into consideration of high prevalence of resistant strains and changing antibiotic susceptibility trends we could conclude that a broad spectrum empirical antibiotic like BLBLI has to be chosen as an initial drug of choice.

Our study has put in place many factors that would influence the clinical outcome like timing of antibiotics and duration of antibiotics. From the above study we could get a picture of the existing battle between gram negative bacteria and antibacterial agents. In such situations we clinicians are posed on a burden to stand guard both existing antibiotics and ensuring clinical cure in patients without compromising quality of care, economic and social factors. With this results we could make changes in the existing hospital policy and keep an eye on a better antibiotic stewardship.

BIBLIOGRAPHY

1. Wilson J, Elgohari S, Livermore DM, Cookson B, Johnson A, Lamagni T, Chronias A, Sheridan E. Trends among pathogens reported as causing bacteraemia in England, 2004–2008. Clinical Microbiology and Infection. 2011 Mar 31;17(3):451-8.

2. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. Euro surveillance: bulletin Europeen sur les maladies transmissibles= European communicable disease bulletin. 2008 Nov;13(47):5437-53.

3. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. JOURNAL OF INTERNAL MEDICINE-OXFORD-. 1998 Nov 1;244:379-86.

4. Tehrani MS, Hajage D, Fihman V, Tankovic J, Cau S, Day N, Visseaux C, Carbonnelle E, Kouatchet A, Cattoir V, Nhan TX. Gram-negative bacteremia: Which empirical antibiotic therapy?. Médecine et maladies infectieuses. 2014 Apr 30;44(4):159-66..

5. Deen J, von Seidlein L, Andersen F, Elle N, White NJ, Lubell Y. Community-acquired bacterial bloodstream infections in developing countries in south and southeast Asia: a systematic review. The Lancet infectious diseases. 2012 Jun 30;12(6):480-7.

6. De Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, Icket C, Kalenic S, Horvatic J, Seifert H, Kaasch A. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. Journal of antimicrobial chemotherapy. 2011 Feb 1;66(2):398-407.

7. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical Infectious Diseases. 2009 Jan 1;48(1):1-2.

8. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS. The third international consensus definitions for sepsis and septic shock (sepsis-3). Jama. 2016 Feb 23;315(8):801-10.

9. Elliott TS. Line-associated bacteraemias. Communicable disease report. CDR review. 1993 Jun;3(7):R91-6.

10. Tille P. Bailey & Scott's diagnostic microbiology. Elsevier Health Sciences; 2013 Aug 13.

11. Bush K. Bench-to-bedside review: The role of β-lactamases in antibiotic-resistant Gram-negative infections. Critical Care. 2010 Jun 29;14(3):1.

12. McGowan JE. Resistance in nonfermenting gram-negative bacteria: multidrug resistance to the maximum. The American journal of medicine. 2006 Jun 30;119(6):S29-36.

13. Bradford PA. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clinical microbiology reviews. 2001 Oct 1;14(4):933-51.

14. Livermore DM. Current epidemiology and growing resistance of gram-negative pathogens. The Korean journal of internal medicine. 2012 May 31;27(2):128-42.

15. Deshpande P, Rodrigues C, Shetty A, Kapadia F, Hedge A, Soman R. New Delhi Metallo-lactamase (NDM-1) in enterobacteriaceae: treatment

options with carbapenems compromised. Journal of Association of Physicians of India. 2010 Mar;58(3):147-9.

16. Sligl W, Taylor G, Brindley PG. Five years of nosocomial Gram-negative bacteremia in a general intensive care unit: epidemiology, antimicrobial susceptibility patterns, and outcomes. International journal of infectious diseases. 2006 Jul 31;10(4):320-5.

17. Al-Hasan MN, Eckel-Passow JE, Baddour LM. Impact of healthcare-associated acquisition on community-onset Gram-negative bloodstream infection: a population-based study. European journal of clinical microbiology & infectious diseases. 2012 Jun 1;31(6):1163-71.

18. Abhilash KP, Veeraraghavan B, Abraham OC. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India. J Assoc Physicians India. 2010 Dec;58(Suppl):13-7.

19. Mohan N , Dutt A S . Antibiogram for a tertiary hospital in kerala . International journal of pharmacological science, 39(2), July – August 2016; 198-201.

20. Graff LR, Franklin KK, Witt L, Cohen N, Jacobs RA, Tompkins L, Guglielmo BJ. Antimicrobial therapy of gram-negative bacteremia at two university-affiliated medical centers. The American journal of medicine. 2002 Feb 15;112(3):204-11.

21. Vidal F, Mensa J, Almela M, Olona M, Martinez JA, Marco F, Lopez MJ, Soriano A, Horcajada JP, Gatell JM, Richart C. Bacteraemia in adults due to glucose non-fermentative Gram-negative bacilli other than P. aeruginosa. QJM. 2003 Mar 1;96(3):227-34.

22. National Treatment Guidelines for Antimicrobial Use in Infectious Diseases http://www.ncdc.gov.in/writereaddata/linkimages/AMR_guideline7001495889.pdf

23. John Hopkins antibiotic guidelines 2015-2016 **www.hopkinsmedicine.org/amp/guidelines/antibiotic_guidelines.pdf**

24. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive care medicine. 2013 Feb 1;39(2):165-228.

25. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clinical microbiology reviews. 2012 Jul 1;25(3):450-70.

26. Chow JW, Victor LY. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. International journal of antimicrobial agents. 1999 Jan 31;11(1):7-12.

27. Kollef MH. Broad-spectrum antimicrobials and the treatment of serious bacterial infections: getting it right up front. Clinical Infectious Diseases. 2008 Sep 15;47(Supplement 1):S3-13.

28. Korvick JA, Bryan CS, Farber B, Beam TR, Schenfeld L, Muder RR, Weinbaum D, Lumish R, Gerding DN, Wagener MM. Prospective observational study of Klebsiella bacteremia in 230 patients: outcome for antibiotic combinations versus monotherapy. Antimicrobial agents and chemotherapy. 1992 Dec 1;36(12):2639-44.

29. Abhilash KP, Veeraraghavan B, Abraham OC. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase

(ESBL)-producing Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India. J Assoc Physicians India. 2010 Dec;58(Suppl):13-7.

30. Shiber S, Yahav D, Avni T, Leibovici L, Paul M. β-Lactam/β-lactamase inhibitors versus carbapenems for the treatment of sepsis: systematic review and meta-analysis of randomized controlled trials. Journal of Antimicrobial Chemotherapy. 2015 Jan 1;70(1):41-7.

31. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, Mulazimoglu L, Trenholme G, Klugman KP, Bonomo RA, Rice LB. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum β-lactamase production in nosocomial infections. Annals of internal medicine. 2004 Jan 6;140(1):26-32.

32. Vasilev K, Reshedko G, Orasan R, Sanchez M, Teras J, Babinchak T, Dukart G, Cooper A, Dartois N, Gandjini H, Orrico R. A Phase 3, open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including Enterobacter species, Acinetobacter baumannii and Klebsiella pneumoniae. Journal of Antimicrobial Chemotherapy. 2008 Sep 1;62(suppl 1):i29-40.

33. Falagas ME, Kasiakou SK, Saravolatz LD. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clinical infectious diseases. 2005 May 1;40(9):1333-41.

34. Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old

antibiotic. Clinical microbiology and infection. 2005 Feb 1;11(2):115-21.

35. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis. Journal of antimicrobial chemotherapy. 2012 Aug 21:dks301.

36. Tamma PD, Han JH, Rock C, Harris AD, Lautenbach E, Hsu AJ, Avdic E, Cosgrove SE. Carbapenem Therapy is Associated with Improved Survival Compared to Piperacillin-Tazobactam for Patients with ESBL Bacteremia. Clinical Infectious Diseases. 2015 Jan 13:civ003.

37. Radji M, Fauziah S, Aribinuko N. Antibiotic sensitivity pattern of bacterial pathogens in the intensive care unit of Fatmawati Hospital, Indonesia. Asian Pacific journal of tropical biomedicine. 2011 Feb 28;1(1):39-42.

38. Balan k , sujitha k , Antibiotic Susceptibility Pattern of Gram Negative Clinical Isolates in a Teaching Tertiary Care Hospital Sch. J. App. Med. Sci., 2013; 1(2):76-79

39. Gandra S, Mojica N, Klein EY, Ashok A, Nerurkar V, Kumari M, Ramesh U, Dey S, Vadwai V, Das BR, Laxminarayan R. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. International Journal of Infectious Diseases. 2016 Sep 30;50:75-82.

40. Rajeevan S, Ahmad SM, Jasmin PT. Study of prevalence and antimicrobial susceptibility pattern in blood isolates from a tertiary care hospital in North Kerala, India. Int J Curr Microbiol App Sci. 2014;3:655-2.

41. Singh AK, Venkatesh V, Singh RP, Singh M. Bacterial and antimicrobial resistance profile of bloodstream infections: A hospital-based study. CHRISMED Journal of Health and Research. 2014 Jul 1;1(3):140.

42. Vanitha Rani N, Gopal K, Venkata Narendra M, Vishwakanth D, Nagesh VR, Yogita M. A retrospective study on blood stream infections and antibiotic susceptibility patterns in a tertiary care teaching hospital. Int J Pharm Pharm Sci. 2012;4(1):543-48.

43. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, Barchuk W. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clinical infectious diseases. 2004 Jan 15;38(2):284-8.

44. Leibovici L, Drucker M, Konigsberger H, Samra Z, Harrari S, Ashkenazi S, Pitlik SD. Septic shock in bacteremic patients: risk factors, features and prognosis. Scandinavian journal of infectious diseases. 2009 Jul 8.

45. Behrendt G, Schneider S, Brodt HR, Just-Nübling G, Shah PM. Influence of antimicrobial treatment on mortality in septicemia. Journal of chemotherapy. 2013 Jul 18.

46. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical care medicine. 2006 Jun 1;34(6):1589-96.

47. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrobial agents and chemotherapy. 2010 Nov 1;54(11):4851-63.

48. Joo EJ, Kang CI, Ha YE, Park SY, Kang SJ, Wi YM, Lee NY, Chung DR, Peck KR, Song JH. Impact of inappropriate empiric antimicrobial therapy on outcome in Pseudomonas aeruginosa bacteraemia: a stratified analysis according to sites of infection. Infection. 2011 Aug 1;39(4):309-18.

49. Zaragoza R, Artero A, Camarena JJ, Sancho S, Gonzalez R, Nogueira JM. The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in an intensive care unit. Clinical microbiology and infection. 2003 May 1;9(5):412-8.

50. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. The American journal of medicine. 2003 Nov 30;115(7):529-35.

51. Grissom CK, Brown SM, Kuttler KG, Boltax JP, Jones J, Jephson AR, Orme JF. A modified sequential organ failure assessment score for critical care triage. Disaster medicine and public health preparedness. 2010 Dec 1;4(04):277-84.

52. Rubinson L, Knebel A, Hick JL. MSOFA: An important step forward, but are we spending too much time on the SOFA?. Disaster medicine and public health preparedness. 2010 Dec 1;4(04):270-2.

53. Halim DA, Murni TW, Redjeki IS. Comparison of Apache II, SOFA, and Modified SOFA scores in predicting mortality of surgical patients in intensive care unit at Dr. Hasan Sadikin General Hospital. Crit Care Shock. 2009;12:157-69.

ANNEXURES

STUDY PROFORMA

1. IP NUMBER: DATE OF ADMISSION / DISCHARGE
2. SEX
3. AGE:
4. TIME OF ARIVAL TO ER:
5. COMORBID CONDITIONS:
6. INITIAL DIAGNOSIS :
7. EMPIRICAL ANTIBIOTIC STARTED:
8. TIME FROM S/O SEPSIS TO FIRST DOSE OF ANTIBIOTIC:
9. NO. OF BLOOD CULTURE SAMPLES SENT:
10. TYPE OF GRAM NEGATIVE ORGANISM GROWN:
11. SENSITIVE TO:
12. RESISTANT TO:
13. ANTIBIOTIC STARTED:
14. MONOTHERAPY OR COMBINATION THERAPY:

15. DURATION OF ANTIBIOTICS:

16. DOSE OF ANTIBIOTICS:

17. LENGTH OF HOSPITAL STAY:

18. COMPLICATIONS DURING STAY:

19. MSOFA SCORE

INITIAL:

REPEAT:

20. CLINICAL OUTCOME

21. FINAL DIAGNOSIS

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

I ----- , POST GRADUATE, M.D GENERAL MEDICINE am carrying out a study on the topic:

"STUDY ON EPIDEMIOLOGY, ANTIBIOTIC SUSCEPTIBILITY AND THE IMPACT OF APPROPRIATE INITIAL ANTIBIOTIC THERAPY ON THE CLINICAL OUTCOME OF GRAM NEGATIVE BACTERAEMIA IN A TERTIARY CARE HOSPITAL"as part of my research project being carried out under the aegis of the Department of: GENERAL MEDICINE

My research guide is: DR.TOLSTOY.R

The justification for this study is:

Emerging antibiotic resistance being a great burden on mortality and morbidity in present era such studies might enable us to frame an institutional policy on appropriate empirical antibiotic choice and guideline on usage of antibiotics based on the antibiotic susceptibility pattern and outcome.

The objectives of this study are:

Primary Objective:

Gram negative bacteremia and their impact on clinical outcome among hospitalised patients

Secondary objective:

To determine the prevalence, antibiotic susceptibility , empirical antibiotic initiation and their impact on morbidity and mortality among hospitalised patients

Sample size: 60

Study volunteers / participants are: GENERAL MEDICAL WARD AND MEDICAL ICU PATIENTS , > 18 YEARS OF AGE.

Location: PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Initial interview: 15 minutes.

Data collected will be stored for a period of 3 years. We will not use the data as part of another study.

Blood sample collection: Specify quantity of blood being drawn:10 ml.

No. of times it will be collected: TWICE

Whether blood sample collection is part of routine procedure or for research (study) purpose:

1. Routine procedure 2. Research purpose

Specify **purpose**, discomfort likely to be felt and side effects, if any: _NO SIDE EFFECTS_

Whether blood sample collected will be stored after study period: Yes / **No, it will be destroyed**

Whether blood sample collected will be sold: Yes / **No**

Whether blood sample collected will be shared with persons from another institution: Yes / **No**

Medication given, if any, duration, side effects, purpose, benefits: **NA**

Whether medication given is part of routine procedure: Yes / No (If not, state reasons for giving this medication)

Whether alternatives are available for medication given: Yes / No (If not, state reasons for giving this particular medication)

Final interview (specify approximate duration):15 MINS -- mts. If **photograph** is taken, purpose: NO

Risks involved by participating in this study : NO RISKS

How the **results** will be used: To study the pattern of drug sensitivity and also the clinical outcome based on the appropriateness of antibiotic used therby preventiing multidrug resistance organisms in becoming a greater threat in coming years .

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date:

Witness:

ABBREVIATIONS

GNB	-	Gram Negative Bacteria
PBP	-	Penicillin Binding Protein
ICU	-	Intensive Care Unit
MSOFA	-	Modified Sequential Organ Failure Assessment
SIRS	-	Systemic Inflammatory Response Syndrome
SOFA	-	Sepsis Related Organ Failure Assessment
qSOFA	-	quick Sepsis Related Organ Failure Assessment
MDR	-	Multidrug Resistant
BLBLI	-	Beta Lactam Beta Lactamase Inhibitor
BSI	-	Blood Stream Infections
RCT	-	Randomized Control Trial
ESBL	-	extended spectrum beta lactamase

LIST OF FIGURES AND TABLES

TABLES

MASTER CHART

AGE	SEX	EMPERICAL ANTIBIOTIC CODE	APPROPRIATENESS	TIME TO FIRST DOSE IN HOURS	TIME TO FIRST DOSE CODED	ORGANISM CODES	DURATION CODE	LENGTH OF HOPSITAL STAY	MSOFA INITIAL	MSOFA REPEAT	CLINICAL OUTCOME CODE
61	F	0	A	2	1	0,4	1	4	0	0	I
50	M	1	IA	3	2	2	1	30	14	14	NI
60	M	1	A	4	2	0	0	10	8	10	NI
65	M	1	IA	5	2	3	1	18	14	14	NI
60	F	1	IA	3	2	0,4	1	15	13	16	NI
55	M	2	IA	4	2	3,6	0	9	12	14	NI
75	F	1	A	2	1	0	0	8	1	0	I
23	F	0	A	2	1	7	1	12	3	0	I
70	F	2	IA	7	2	3	1	18	8	12	NI
21	F	1	IA	4	2	0,4,5	0	7	6	9	NI
56	F	2	A	4	2	0,4	1	10	5	1	I
58	F	2	IA	4	2	7,4,5	1	9	2	0	I
95	M	1	IA	3	2	0,4,5	0	8	2	2	NI
58	F	1	IA	3	2	0,4	0	8	2	2	NI
58	M	0	A	5	2	0	1	9	4	2	I
64	F	2	A	2	1	0	1	16	8	2	I
85	M	2	A	2	1	0	0	13	4	2	I

69	F	1	A	2	1	1	0	10	2	0	I
64	M	2	A	3	1	0,4	1	10	4	2	I
67	F	0	A	4	2	0,4	1	28	10	4	I
65	M	1	IA	6	2	0,4	1	15	14	14	NI
65	M	1	IA	4	2	0,4,5	0	12	4	21	NI
52	M	2	IA	4	2	0,4,5	0	15	12	14	NI
76	F	1	A	3	1	1	1	10	4	0	I
63	F	0	A	3	1	0	1	8	4	2	I
78	M	1	A	3	1	0	0	8	2	0	I
59	M	1	IA	5	2	0,4,5	0	15	4	8	NI
67	F	3	A	3	1	0,4	1	14	4	0	I
55	F	2	A	4	2	0,4,5	0	2	12	14	NI
57	F	1	IA	4	2	1,6	0	25	12	14	NI
20	F	1	IA	4	2	0,4	0	7	2	0	I
62	F	1	A	3	1	0	1	7	2	0	I
60	M	2	IA	2	1	1,2	1	25	12	14	NI
24	M	0	A	3	1	0	1	4	4	1	I
60	F	2	A	1	0	0,4	1	9	4	1	I
70	M	2	A	1	0	0,4	1	7	4	1	I
70	M	0	A	3	1	0	1	9	2	0	I
31	M	1	A	4	2	1	0	9	4	0	I
65	F	3	A	1	0	0	1	10	4	1	I

45	F	3	A	2	1	0,4	1	9	10	2	I
67	F	0	A	3	1	0,4	1	4	4	0	I
76	F	1	IA	5	2	2	0	30	9	11	NI
48	F	3	A	3	1	1,4	1	10	2	1	I
80	M	3	A	3	1	1,4	1	14	2	1	I
64	F	1	A	3	1	0	1	16	3	1	I
58	F	2	A	4	2	0,4	1	10	4	0	I
50	F	2	A	3	1	0,4	1	11	4	0	I
82	F	1	IA	5	2	1,4,5	0	7	8	10	NI
60	F	2	A	2	1	0,4	1	9	3	0	I
65	F	1	IA	3	1	0,4	1	11	3	1	I
60	F	1	A	4	2	1	0	12	4	6	NI
68	F	1	IA	4	2	2	0	7	2	2	NI
47	M	2	A	3	1	0,4	1	14	6	0	I
72	F	1	A	3	1	1	0	7	0	0	I
67	F	1	IA	4	2	0,4	0	10	2	2	NI
60	M	2	A	3	1	0	1	7	2	0	I
70	M	1	IA	2	1	0,4	1	16	6	1	I
71	M	1	IA	4	2	0,4	1	7	4	0	I
60	M	1	IA	5	2	0,4	1	16	6	0	I
50	M	3	A	2	1	1	1	14	8	16	NI

MASTER SHEET - KEY

EMPIRICAL ANTIBIOTIC STARTED

APPROPRIATE – A

INAPPROPRIATE – IA

CEFOPREAZONE SULBACTAM – 0

CEFTRIAXONE -1

PIPREACILLIN TAZOBACTEM -2

MEROPENEM- 3

TIME TO FIRST DOSE OF ANTIBIOTIC

<1 HR- 0

1-3 HR-1

>3 HR-2

DURATION OF ANTIBIOTIC

<7 DAYS -0

>7 DAYS-1

TYPE OF ORGANISMS

E.COLI-0

K.PNEUMONIAE-1

P.AURIGINOSA-2

A.BAUMANI-3

ESBL-4

AMPC-5

CARBAPENAMASE-6

OTHER -7

CLINICAL OUTCOME

IMPROVED-I

NOT IMPROVED -NI